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SEPTEMBER 18, 1990

A Symposium: HMG CoA Reductase Inhibitors — A Five-Year Clinical Perspective

GUEST EDITOR:
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Chairman, Department of Clinical Nutrition
Director, Center for Human Nutrition
Professor of Internal Medicine and Biochemistry
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Dallas, Texas

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Efficacy and Tolerability of Lovastatin in a Six-Month Study: Analysis by Gender, Age and Hypertensive Status

William B. Kannel, MD, Ralph B. D'Agostino, PhD, Miganush Stepanians, MA,
and LeiLanie C. D'Agostino, BA

This study reports the results of a 6-month, open-label multicenter study of the efficacy and tolerability of lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor, in the management of nonfamilial primary hypercholesterolemia. The study enrolled 489 patients with elevated total serum cholesterol levels, whose lipids were not controlled sufficiently by diet. There was good representation of gender (48.3% women and 51.7% men), age (mean 57, range 25 to 83) and hypertension status (55.4% normotensive and 43.6% hypertensive) in the sample.

Within 1 month of lovastatin therapy, total cholesterol was reduced 19% (from a mean of 269 to 217 mg/dl, low-density lipoprotein (LDL) cholesterol was reduced 27% (191 to 140 mg/dl), high-density lipoprotein (HDL) cholesterol increased 6% (42.6 to 45.1 mg/dl), the ratio of total cholesterol to HDL was reduced 24% (6.7 to 5.1) and the ratio of LDL to HDL was reduced 30% (4.7 to 3.3). These results were consistent across age group, gender and hypertension status, and were maintained for a period of 6 months of therapy.

Lovastatin was generally well tolerated. Of the 489 patients enrolled, 449 (92%) completed 6 months of therapy. Only 21 (4%) withdrew because of adverse experience regardless of cause. None of the few serious adverse experiences (e.g., myocardial infarction) could be attributed to the drug. Abnormal laboratory values during the 6 months of therapy were within expectations. Seventy-four patients had at least 1 abnormal value during 6 months of treatment. Of these, 42 had at least 1 mild to moderate creatine phosphokinase elevation during this period. Only 1 patient had an adverse change on ophthalmologic examination: a posterior subcapsular opacity in both eyes just visible on 6-month examination.

(Am J Cardiol 1990;66:1B–10B)

With the availability of a variety of agents that generally are effective in the management of abnormal serum lipids, and with evidence from controlled clinical trials of the benefit of this management in the control of coronary artery disease (CAD), interest in the control of blood lipids has been renewed.[1] Epidemiologic evidence of the importance of serum cholesterol in the evolution of CAD is now widely accepted.[1,2] The major concern now is when and how to treat patients with abnormal blood lipids, rather than whether to treat them.

A multicenter, 6-month, open-label study was conducted to evaluate the efficacy and tolerability of lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, in the management of nonfamilial primary hypercholesterolemia. This study reports on the design and results of that study, with emphasis on age, gender and hypertensive status of the patients studied.

METHODS

Design: The design was a multicenter, open-label, prospective study involving 40 centers (Table I). On visit 1, a complete history was taken and a physical evaluation that included ophthalmologic examination was performed. Laboratory studies included a complete blood count with white blood count and differential; serum electrolytes; blood chemistry including blood urea nitrogen, creatinine, glucose, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, bilirubin, creatine phosphokinase and T4; serum lipid profile; urinalysis; and electrocardiogram.

On visit 2, patients older than 21 who were not receiving a cholesterol-reducing diet, and whose total cholesterol level was between 240 and 300 mg/dl with (1) low-

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From the Boston University School of Medicine, Department of Preventive Medicine (WB Kannel) and Boston University Mathematics Department and Boston University Statistics and Consulting Unit. This study was supported by a grant from Merck Sharp & Dohme, West Point, Pennsylvania.

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TABLE I Principal Investigators in Six-Month Study of Lovastatin Therapy in the Management of Nonfamilial Primary Hypercholesterolemia

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TABLE I Principal Investigators in Six-Month Study of Lovastatin Therapy in the Management of Nonfamilial Primary Hypercholesterolemia

Investigator	Location
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James A. Schumacher, MD	Good Samaritan Hospital Phoenix, AZ
Thorne Sparkman, MD	University of Pennsylvania School of Medicine Philadelphia, PA
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Jonathan M. Tobis, MD & Nathan D. Wong, PhD	University of California Irvine Medical Center Orange, CA
Joseph S. Wilson, MD	Emory University School of Medicine Atlanta, GA

density lipoprotein (LDL) cholesterol levels ≥190, or (2) LDL cholesterol levels ≥160 mg/dl with definite CAD or 2 other CAD risk factors, were given a standard cholesterol-reducing diet and all lipid-lowering agents were withdrawn for at least 6 weeks.

After the diet-only (baseline) period, each patient's lipid profile was evaluated on visits 3 and 4. Patients with (1) LDL ≥190 mg/dl, or (2) LDL ≥160 mg/dl with definite CAD or 2 other CAD risk factors, for whom further attempts to reduce serum cholesterol by diet and other nonpharmacologic measures alone were considered insufficient, were enrolled in the diet plus lovastatin treatment phase. A total of 489 patients were enrolled in the study. The initial dosage of lovastatin was 20 mg/day with the evening meal. Patients continued on the cholesterol-lowering diet and were evaluated every month during the 6-month treatment period with lovastatin (visits 5 to 10). Evaluations included clinical assessment, serum lipid profile, blood studies, and the recording of any adverse effects. On the last visit, an ophthalmologic examination was also performed. The dosage of lovastatin could be adjusted at monthly intervals according to the response of the patient, up to a maximum of 80 mg/day in a single dose or 2 equally divided doses with meals.

Patients were excluded if cholesterol was controlled by diet alone, if they were hypersensitive to any component of lovastatin, if dietary therapy was impractical or inadvisable (e.g., for certain malnourished or elderly patients), if they had active liver disease or unexplained persistent elevation of serum transaminases, or if they were premenopausal unless surgically sterilized (tubal ligation or hysterectomy).

Lipid analysis: Serum lipids were measured at all visits. Total serum cholesterol was measured by the method described by Trinder[3] and Allain et al,[4] triglycerides by the procedure of Esders and Micheina,[5] and high-density lipoprotein (HDL) cholesterol by the method described by Burstein et al.[6] All lipid analyses were performed by a central laboratory, SmithKline Bio-Science Laboratories, Van Nuys, California.

Efficacy variables: The lipid variables under consideration were total cholesterol, LDL, HDL, very low density lipoprotein (VLDL) cholesterol, triglycerides, the ratio of total to HDL cholesterol, and the ratio of LDL to HDL cholesterol. Responses were defined as changes from baseline for these lipid variables. Baseline values were postdiet–only values.

The changes observed after 1 month of lovastatin therapy were of primary interest. The maintenance of the 1-month changes over the entire 6-month treatment period were also of interest.

Patient groups for analysis: Reduction in serum cholesterol for all the patients combined and the reductions in various subgroups were assessed. The subgroups analyzed were men, women, normotensive and hypertensive patients, and 10-year age groups (e.g., 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79).

Statistical analysis: The paired *t* test was used to test whether cholesterol levels after lovastatin therapy showed significant improvement over baseline values. The two independent sample *t* tests and analysis of covariance were used to compare men and women. Changes from baseline were the dependent variables. The covariates employed were baseline cholesterol and age. The two independent sample *t* tests and the analysis of covariance were also used to compare normotensive and hypertensive patients. The covariates employed were baseline cholesterol, age and gender. All tests were 2-tailed. The 1-way analysis of variance was used to compare the incremental changes across age groups. The 0.05 level was used in all cases for the declaration of statistical significance.

Safety evaluation: At each monthly visit, the full battery of blood tests described earlier was performed and detailed information on adverse effects obtained. At en-

TABLE II Gender, Age and Hypertension Status of Study Patients at Baseline (n = 489)

	No. of Pts.	%
Women	236	48.3
Men	253	51.7
Age (yr)		
20–29	3	0.6
30–39	38	7.8
40–49	77	15.7
50–59	142	29.0
60–69	156	31.9
70–79	67	13.7
80–90	4	0.8
Missing	2	0.4
Mean ± SD	57 ± 11	
Youngest	25	
Oldest	83	
Hypertension status		
Normotensive	271	55.4
Hypertensive	213	43.6
Missing	5	1.0

SD = standard deviation.

try, and at the end of the study, a complete ophthalmologic evaluation, including slit-lamp examination, was performed.

RESULTS

Baseline: The study enrolled 489 patients with elevated serum total cholesterol whose lipids were not controlled sufficiently by diet. There were 236 women (48.3%) and 253 men (51.7%) aged 25 to 83 years (mean ± standard deviation [SD] 57 ± 11) (Table II). Of these, 55.4% were normotensive and 43.6% were hypertensive patients.

There was a high frequency of other cardiovascular risk factors in the patients studied (Table III). Two-hundred thirty-nine (48.9%) reported a family history of premature CAD. Seventeen percent smoked cigarettes, 21.3% had low HDL cholesterol (i.e., <35 mg/dl), 7.4% had diabetes, 9.2% had a history of definite cerebrovascular or occlusive peripheral vascular disease, and 10.8% were obese (i.e., at least 30% over ideal weight).

TABLE III Coronary Risk Factors of Study Patients at Baseline (n = 489)[*]

	No. of Pts.	%
Family history of premature coronary artery disease		
No	239	48.9
Yes	239	48.9
Cigarette smoking (more than 10 a day)		
No	402	82.2
Yes	83	17.0
Low HDL cholesterol (<35 mg/dl)		
No	324	66.3
Yes	104	21.3
Diabetes mellitus		
No	450	92.0
Yes	36	7.4
History of definite cerebrovascular or occlusive peripheral vascular disease		
No	432	88.3
Yes	45	9.2
Severe obesity (greater than 30% overweight)		
No	421	86.1
Yes	53	10.8

[*] Values of numbers not adding to 489 are due to missing values.
HDL = high-density lipoprotein.

TABLE IV Cholesterol data[*]: Baseline, One-Month After Lovastatin Therapy (Visit 5), and One-Month Changes

	Baseline	Visit 5[†]	Visit 5—Baseline Adjusted Mean	p[‡]
Total cholesterol				
Mean	269	217	−52	0.0001
SD	27	32	29	
LDL cholesterol				
Mean	191	140	−51	0.0001
SD	26	29	27	
HDL cholesterol				
Mean	42.6	45.1	+2.4	0.0001
SD	11	11	6.5	
Total/HDL cholesterol ratio				
Mean	6.67	5.09	−1.6	0.0001
SD	1.6	1.4	1.1	
LDL/HDL cholesterol ratio				
Mean	4.74	3.29	−1.4	0.0001
SD	1.3	1.1	0.9	
VLDL cholesterol				
Mean	35.6	32.1	−3.7	0.0001
SD	16	16	12	
Triglycerides				
Mean	178	161	−18	0.0001
SD	83	83	62	

[*] Units for all cholesterol variables are mg/dl.

[†] 488 patients attended visit 5. For each of the *t* tests, data on at least 472 patients were available.

[‡] p levels are for 2-tailed paired *t* test testing that 1 month increments are different than zero.

HDL = high density lipoprotein; LDL = low-density lipoprotein; VLDL = very low density lipoprotein.

Table IV contains summary data for the baseline lipoprotein cholesterol values. Mean total cholesterol ± SD was 269 ± 27 mg/dl, mean LDL cholesterol was 191 ± 26 mg/dl and mean HDL cholesterol was 42.6 ± 11 mg/dl. Mean ratio of total to HDL cholesterol was 6.67 ± 1.6, whereas mean ratio of LDL to HDL cholesterol was 4.74 ± 1.3. Mean VLDL cholesterol and mean triglycerides were 35.6 and 178 mg/dl, respectively, with SDs of 16 and 83 mg/dl, respectively.

Withdrawals: The number of patients available for analysis at baseline and for each of the 6 months of therapy were 489, 488, 481, 474, 466, 464 and 449, respectively. Forty patients (8%) did not complete the study. These are discussed in the section on safety. For the following, analyses were performed on all patients for whom data were available at the particular time point.

Effectiveness at one-month of therapy—total group: After 1 month of therapy, data on 488 patients were available for efficacy analysis. Table IV lists lipoprotein cholesterol values after 1 month of therapy, and the changes from baseline to 1 month. All patients available for computation are included in Table IV; sample sizes vary since occasionally some lipid values were not obtained from blood samples. Total cholesterol decreased from a baseline mean of 269 mg/dl to a 1-month therapy mean of 217 mg/dl, a highly significant decrease of 52 mg/dl, or 19% ($p = 0.0001$). Changes in the other cholesterol components were also all highly significant ($p = 0.0001$): LDL was reduced 51 mg/dl (27%) to a mean of 140 mg/dl, HDL increased from 42.6 to 45.1 mg/dl for a 6% increase, the ratio of total to HDL cholesterol decreased from 6.67 to 5.09 or 24%, the ratio of LDL to HDL cholesterol decreased from 4.74 to 3.29 for a decrease of 30%, VLDL was reduced 3.7 mg/dl (10%), and triglycerides were reduced 18 mg/dl (10%).

Six-month time course—total group: The 1-month results were sustained over the full 6 months of lovastatin

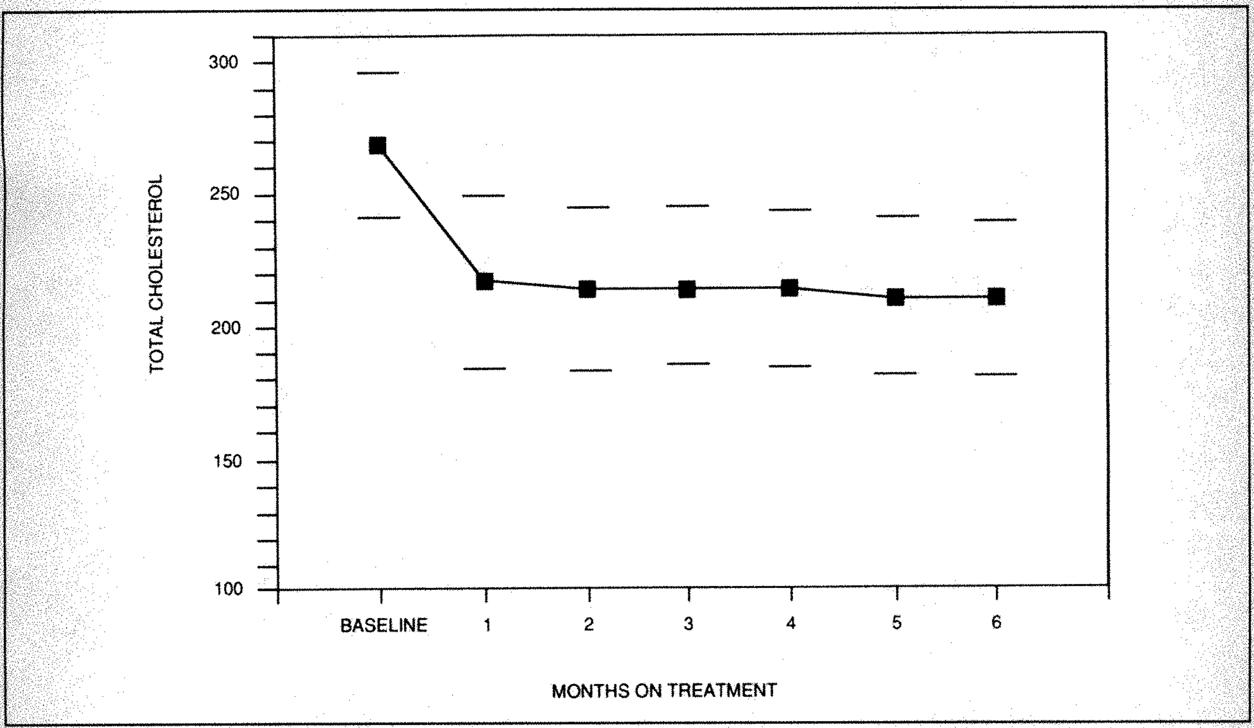

FIGURE 1. Total serum cholesterol response to lovastatin treatment over 6 months (mean ± standard deviation).

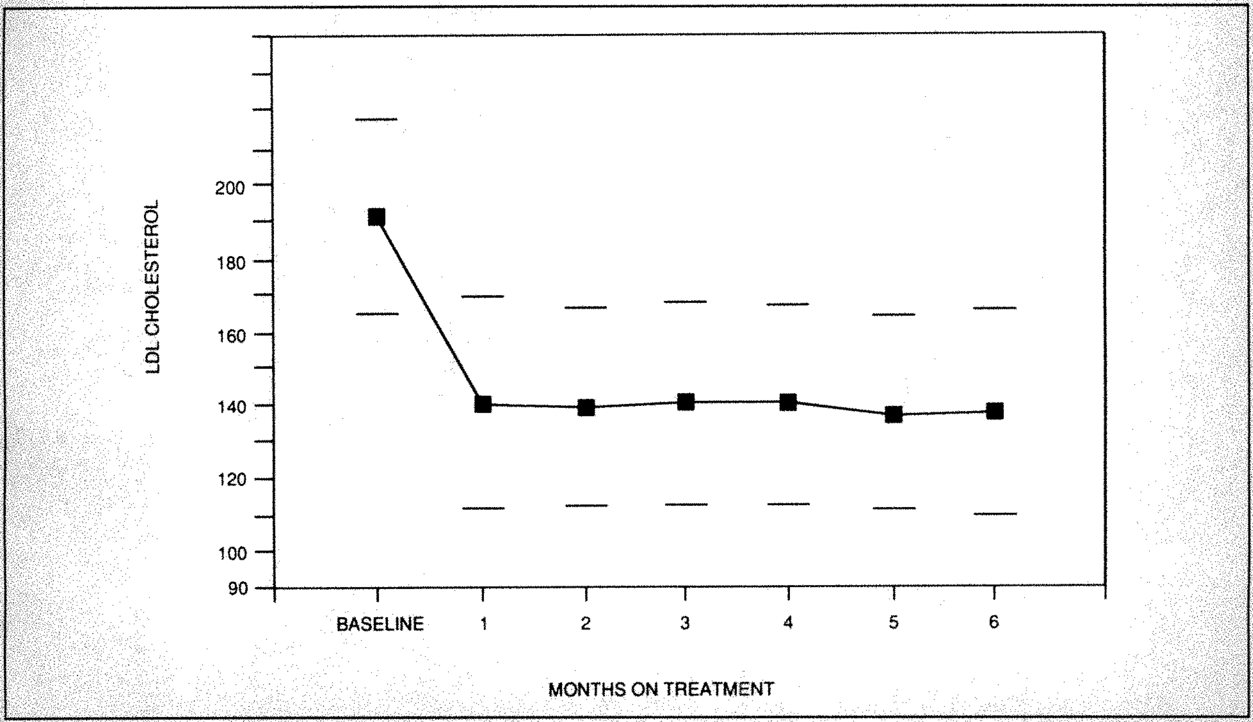

FIGURE 2. Low-density lipoprotein (LDL) cholesterol response to lovastatin treatment over 6 months (mean ± standard deviation).

therapy. Figures 1 through 5 plot mean values for total, LDL and HDL cholesterol; the ratio of total to HDL cholesterol; and the ratio of LDL to HDL cholesterol, respectively, during the 6 months of therapy. Lines representing the SDs are also shown in the figures. There were no significant changes from the 1-month results; once the reduction was attained, generally within 1 month of therapy, it was maintained.

Reduction from high levels—total group: Of 429 patients with total cholesterol ≥240 mg/dl on baseline, 337 (78.6%) had levels <240 mg/dl after 1 month of therapy. Of 437 patients with LDL cholesterol ≥160 mg/dl at

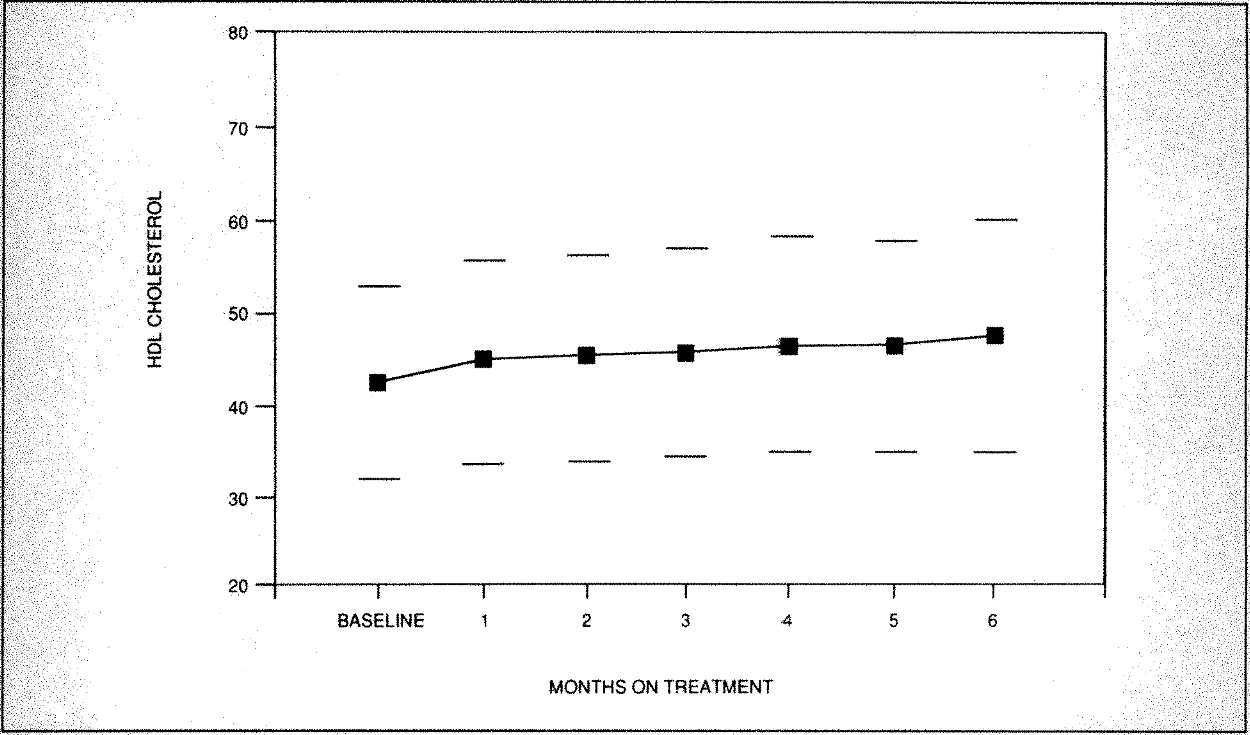

FIGURE 3. High-density lipoprotein (HDL) cholesterol response to lovastatin treatment over 6 months (mean ± standard deviation).

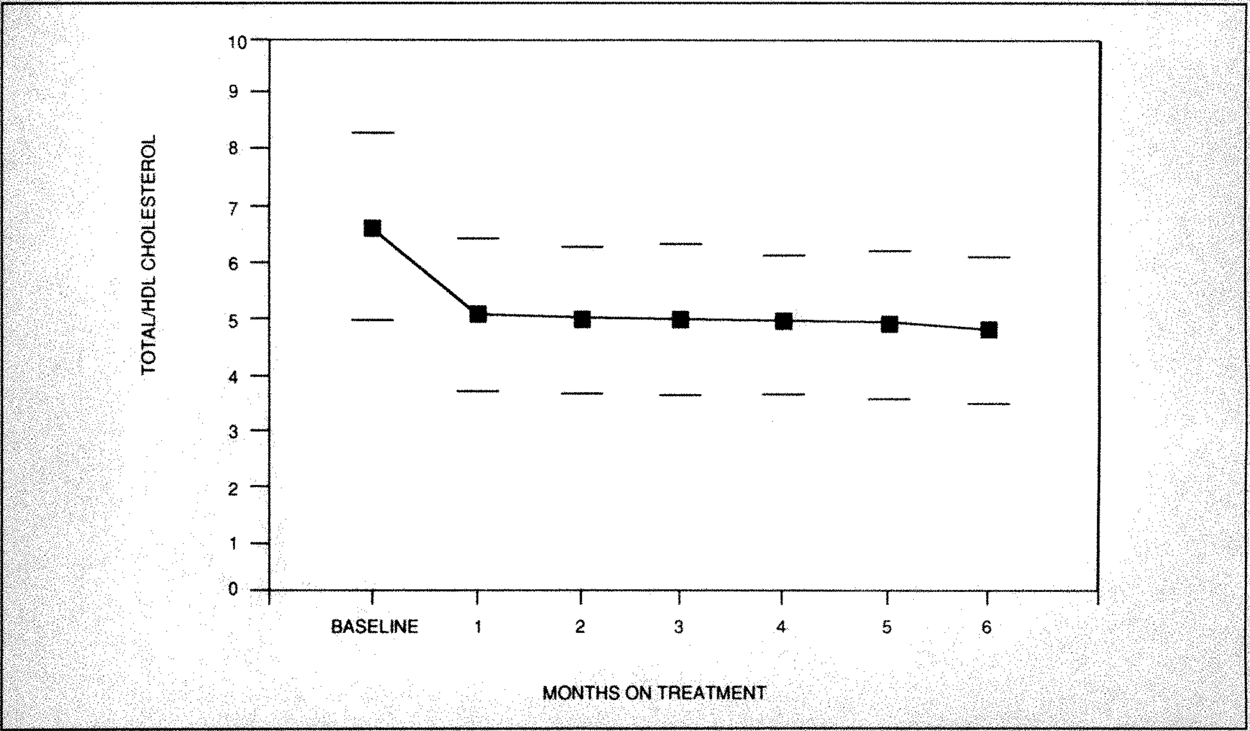

FIGURE 4. Total/high-density lipoprotein (Total/HDL) cholesterol response to lovastatin treatment over 6 months (mean ± standard deviation).

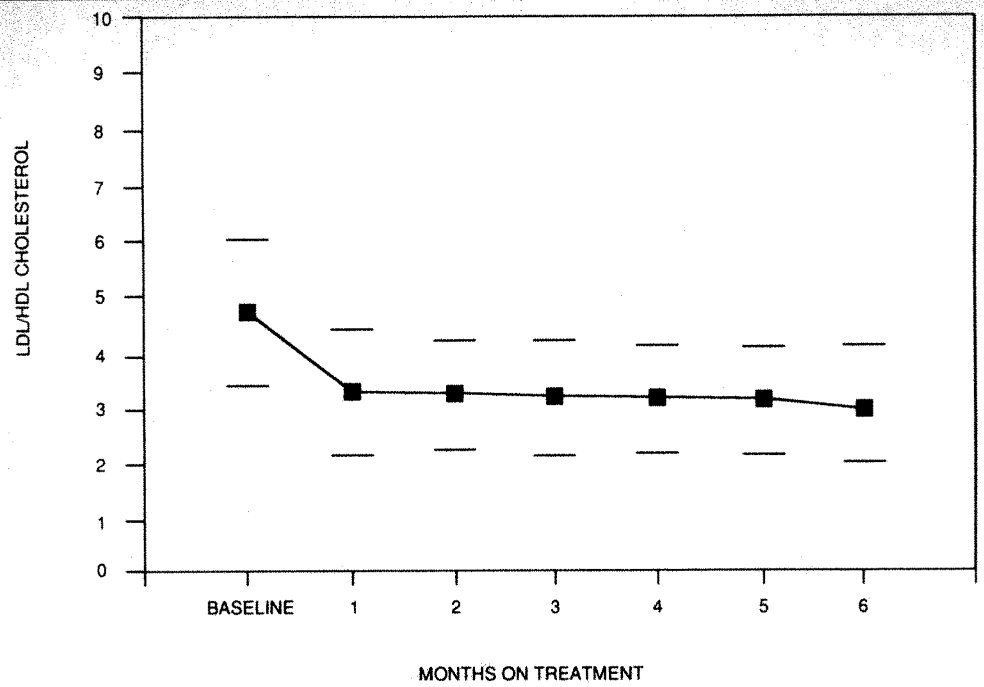

FIGURE 5. Low-density/high-density lipoprotein (LDL/HDL) cholesterol response to lovastatin treatment over 6 months (mean ± standard deviation).

baseline, 343 (78.5%) had reductions to <160 mg/dl after 1 month of therapy. These levels were maintained during 6 months of therapy.

Goal low-density lipoprotein cholesterol achieved—total group: At the end of 6 months of lovastatin therapy, 76.5% of patients with LDL cholesterol ≥190 mg/dl attained a goal LDL level (<160 mg/dl), while 51.8% of patients with LDL levels ≥160 mg/dl and ≤190 mg/dl attained goal LDL (<130 mg/dl). Overall, 60.8% of patients attained desirable goal LDL cholesterol levels. Mean dosage of lovastatin used was 37.4 ± 19 mg/day.

Efficacy results by gender: Lovastatin therapy was effective in both men and women. Table V lists the results of analyses by gender. For men and women, mean baseline cholesterol values and values after 1 month of lovastatin therapy are listed. One-month changes adjusted for baseline and age are also listed. There were significant improvements in both genders (p = 0.0001) for all lipid components. There were no significant differences between male and female patients' responses to treatment except for HDL cholesterol. For this variable, women showed an adjusted increase of 3.1 mg/dl compared with an increase of 1.7 mg/dl in men (p = 0.03). The unadjusted changes are 2.6 and 2.3, which are not significantly different. For women with total cholesterol ≥240 mg/dl at baseline, 77% (167 of 218) had values <240 mg/dl within 1 month; for men, 80% (170 of 211) achieved this. For LDL cholesterol, 80% of women and 78% of the men with LDL cholesterol ≥160 mg/dl at baseline, values were reduced to <160 mg/dl after 1 month of therapy. These results were sustained during 6 months of therapy.

Efficacy results—hypertensive status: Lovastatin therapy was effective for both normotensive and hypertensive patients. Table VI lists, for each group, mean

TABLE V Cholesterol Data* by Gender: Baseline, One-Month After Lovastatin Therapy (Visit 5), and One Month Adjusted Changes (Adjusted for Baseline and Age)

	Baseline Mean	Visit 5† Mean	Visit 5—Baseline Adjusted Mean	Paired *t* Test (p)
Total cholesterol				
Women	275	220	−51	0.0001
Men	264	215	−53	0.0001
p level: adjusted changes equal for women and men p = 0.11				
LDL cholesterol				
Women	193	138	−53	0.0000
Men	189	141	−50	0.0000
p level: adjusted changes equal for women and men p = 0.20				
HDL cholesterol				
Women	46.3	48.9	+3.1	0.0000
Men	39.2	41.5	+1.7	0.0000
p level: adjusted changes equal for women and men p = 0.03				
Total/HDL cholesterol ratio				
Women	6.3	4.7	−1.6	0.0001
Men	7.0	5.4	−1.5	0.0001
p level: adjusted changes equal for women and men p = 0.13				
LDL/HDL cholesterol ratio				
Women	4.4	3.0	−1.5	0.0001
Men	5.0	3.6	−1.4	0.0001
p level: adjusted changes equal for women and men p = 0.14				
VLDL cholesterol				
Women	36	33	−3	0.0004
Men	35	31	−4	0.0001
p level: adjusted changes equal for women and men p = 0.16				
Triglycerides				
Women	180	165	−15	0.0002
Men	177	157	−21	0.0001
p level: adjusted changes equal for women and men p = 0.30				

* Unit for all cholesterol variables is mg/dl.

† 488 patients attended visit 5. For each of the *t* tests and covariance analyses, data on at least 472 patients were available.

Abbreviations as in Table IV.

TABLE VI Cholesterol Data* by Hypertensive Status: Baseline, One-Month After Lovastatin Therapy (Visit 5), and One-Month Adjusted Increments (Adjusted for Baseline, Age and Gender)

	Baseline Mean	Visit 5† Mean	Visit 5—Baseline Adjusted Mean	Paired *t* Test (p)
Total cholesterol				
Normotensive	270	218	−52	0.0001
Hypertensive	268	217	−52	0.0001
p level: adjusted changes equal for normotensive and hypertensive p = 0.83				
LDL cholesterol				
Normotensive	194	143	−51	0.0001
Hypertensive	189	137	−52	0.0001
p level: adjusted changes equal for normotensive and hypertensive p = 0.77				
HDL cholesterol				
Normotensive	42.4	44.4	+2.0	0.0001
Hypertensive	43.0	45.9	+2.7	0.0001
p level: adjusted changes equal for normotensive and hypertensive p = 0.24				
Total/HDL cholesterol ratio				
Normotensive	6.7	5.2	−1.5	0.0001
Hypertensive	6.6	5.0	−1.6	0.0001
p level: adjusted changes equal for normotensive and hypertensive p = 0.44				
LDL/HDL cholesterol ratio				
Normotensive	4.8	3.4	−1.4	0.0001
Hypertensive	4.6	3.1	−1.5	0.0001
p level: adjusted changes equal for normotensive and hypertensive p = 0.26				
VLDL cholesterol				
Normotensive	34	30	−4	0.0001
Hypertensive	38	34	−3	0.0002
p level: adjusted changes equal for normotensive and hypertensive p = 0.52				
Triglycerides				
Normotensive	168	153	−18	0.0001
Hypertensive	191	171	−17	0.0001
p level: adjusted changes equal for normotensive and hypertensive p = 0.83				

* Unit for all cholesterol variables is mg/dl.

† 488 patients attended visit 5. For each of the *t* tests and covariance analyses, data on at least 467 patients were available.

Abbreviations as in Table IV.

values at baseline, after 1 month of therapy and the changes after 1 month for all the lipid variables. The changes are adjusted for baseline values, gender and age. In all cases, highly significant changes were observed after 1 month of therapy (p = 0.0001) compared with baseline and no significant differences were observed between normotensive and hypertensive groups after 1 month. For normotensive patients with total cholesterol ≥240 mg/dl at baseline, 77% (184 of 239) had a reduction to <240 mg/dl after 1 month of therapy. For the hypertensive patients, 80% (149 of 186) achieved this. For LDL cholesterol, 77% (190 of 247) and 80% (150 of 187) of the normotensive and hypertensive patients, respectively, had LDL levels ≥160 mg/dl at baseline and <160 mg/dl by the end of 1 month of therapy.

Efficacy results—age groups: Patients were aged 25 to 83 years (mean ± SD 57 ± 11). Analysis was performed on subgroups according to age (20 to 29, 30 to 39, 40 to 49, ... 80 and older). Table VII contains, for each age group, mean values at baseline, after 1 month of

TABLE VII Cholesterol Data by Age: Baseline, One Month After Lovastatin Therapy (Visit 5), and One-Month Changes

	Baseline		Visit 5		Baseline-visit 5		P value ANOVA*
	Mean	No.	Mean	No.	Mean	No.	
Total Cholesterol							
20–29	253	3	224	3	29	3	0.05
30–39	274	38	225	38	50	38	
40–49	268	77	219	75	50	75	
50–59	266	141	220	142	47	141	
60–69	270	156	214	155	56	155	
70–79	270	67	213	67	57	67	
80 up	267	4	196	4	70	4	
LDL Cholesterol							
20–29	188	3	147	3	41	3	0.005
30–39	199	38	153	36	45	36	
40–49	193	77	144	74	50	74	
50–59	189	140	143	137	47	136	
60–69	191	152	136	152	55	150	
70–79	190	67	134	67	56	67	
80 up	184	4	120	4	63	4	
HDL Cholesterol							
20–29	49	3	48	3	1	3	0.68
30–39	38	38	40	38	−1	38	
40–49	41	77	43	75	−2	75	
50–59	42	141	45	141	−2	140	
60–69	44	156	47	155	−2	155	
70–79	43	67	47	67	−3	67	
80 up	47	4	51	4	−4	4	
VLDL Cholesterol							
20–29	33	3	29	3	4	3	0.06
30–39	37	38	28	38	9	38	
40–49	34	77	30	75	4	75	
50–59	35	141	33	141	2	140	
60–69	36	156	32	155	4	155	
70–79	37	67	33	67	4	67	
80 up	36	4	24	4	11	4	
Triglycerides							
20–29	164	3	147	3	17	3	0.07
30–39	185	38	143	38	43	38	
40–49	169	77	151	75	20	75	
50–59	175	141	169	141	8	140	
60–69	182	156	163	155	19	155	
70–79	183	67	165	67	18	67	
80 up	180	4	123	4	57	4	
Total Cholesterol/HDL Cholesterol							
20–29	5.3	3	4.8	3	0.5	3	0.42
30–39	7.6	38	5.9	38	1.7	38	
40–49	7.0	77	5.4	75	1.6	75	
50–59	6.6	141	5.2	141	1.4	140	
60–69	6.4	156	4.8	155	1.6	155	
70–79	6.4	67	4.7	67	1.7	67	
80 up	5.7	4	3.8	4	1.9	4	
LDL/HDL Cholesterol							
20–29	3.9	3	3.1	3	0.7	3	0.52
30–39	5.5	38	4.0	36	1.4	36	
40–49	5.1	77	3.6	74	1.5	74	
50–59	4.7	140	3.4	137	1.3	136	
60–69	4.5	152	3.1	152	1.5	150	
70–79	4.5	67	3.0	67	1.6	67	
80 up	3.9	4	2.3	4	1.6	4	

* ANOVA = Analysis of variance test is a test of equality of mean increments across age groups; other abbreviations as in Table IV.

TABLE VIII Withdrawals from Study Because of Adverse Clinical Experiences Regardless of Cause

Patient and Adverse Experiences
1. Hair loss and itchy skin
2. Nausea and vomiting
3. Generalized rash/itching
4. Diarrhea
5. Severe constipation/severe fatigue
6. Moderate muscular weakness/aching of lower extremities
7. Muscular pain across anterior chest wall/abdominal cramps
8. Underwent surgery for left ovarian tumor
9. Abdominal cramps, nausea and dizziness
10. Intermittent diarrhea, abdominal cramps/slight chest discomfort
11. Dizziness and nausea
12. Patient known to have coronary artery disease/had acute myocardial infarction and underwent coronary artery bypass surgery.
13. Patient died of coronary artery disease/had previous bypass surgery/known to have coronary artery disease
14. Cancer of prostate/underwent coronary artery bypass surgery
15. Skin rash on chest and under eyes
16. Nausea
17. Headache, dizziness and nightmares
18. Right costal chondritis
19. Chest discomfort
20. Cancer of breast after one month of therapy/patient underwent surgery
21. Muscle ache and flu-like syndrome

Total patients withdrawn = 21.

TABLE IX Clinical Adverse Experiences Regardless of Cause*

	No. of Pts.
Gastrointestinal (abdominal pain, diarrhea, nausea, constipation, gastric distress, vomiting)	33
Musculoskeletal (myalgia, muscle cramps, chest discomfort, fatigue, pain in extremities)	19
Nervous system/psychiatric (headache, dizziness, nervousness, insomnia)	19
Skin (rash, pruritus, herpes, hair loss)	9
Special senses (blurred vision, watery or itching eyes, detached retina, earache, nosebleed, bad taste)	9
Cardiovascular (coronary artery disease,myocardial infarction, coronary bypass surgery, shortness of breath, angina, atrial flutter)	10
Genitourinary (cancer of the prostate, benign prostatic hypertrophy, urinary tenesmus, hematuria, cancer of the ovary)	7
Miscellaneous (cancer of the breast, acute gouty arthritis, chills and fever, cold sweats, nightmares, car accident)	6

* Data in table correspond to number of times adverse experience category was noted over 6 months of lovastatin therapy.
Total number of patients with clinical adverse experience = 85.

therapy, and the changes after 1 month of therapy. The p levels reported in Table VII correspond to 1-way analysis of variance comparing age groups performed on 1-month changes of the lipid parameters. For each age subgroup, the changes in all lipoprotein cholesterol variables are similar to those observed for the combined data. The only variations noted for total, LDL and VLDL cholesterol, and triglycerides are at the extremes of the age groups (i.e., in the 20 to 29 and 80 and older groups). However, sample sizes in these groups were small and generalizations are therefore unwarranted. In general, lovastatin therapy appeared effective in all ages.

Adverse effects—safety evaluation: There were no unusual or unexpected adverse effects attributed to lovastatin in this study. Of the 489 patients enrolled in the study (i.e., those who received lovastatin therapy), 40 (8%) were withdrawn over the period of 6 months. Nineteen patients were withdrawn for reasons other than adverse experiences (i.e., protocol violations, noncompliance, or lost to follow-up). Twenty-one patients were withdrawn because of adverse experiences regardless of cause (Table VIII). The serious occurrences (e.g., surgery for ovarian cancer, coronary artery bypass surgery, death from CAD, prostate cancer and breast cancer) were not attributed to lovastatin therapy by the investigator.

Overall, 85 patients (17%) had at least 1 clinical adverse experience during the 6 months of therapy (i.e., reported on visits 5 to 10). Table IX lists the categories of all clinical adverse experiences reported during the study regardless of cause. There were only 5 complaints of myalgia or muscle cramps over the entire 6 months of therapy.

Of the 489 patients, 74 (15%) had at least 1 laboratory value out of the normal range over the full 6 months of therapy. Of these, 5 had values out of the normal range on baseline examination, or were diabetic, thus explaining these abnormal values during the 6-month therapy period. There were 31 reports of mild to moderate elevation of liver function tests (serum glutamic oxaloacetic transaminase 3, serum glutamic pyruvic transaminase 12, alkaline phosphatase 13, and total bilirubin 3) during 6 months of therapy. Furthermore, during 6 months of the study, 42 patients (8.5%) had mild to moderate elevated creatine phosphokinase (CPK). No patients with elevated CPK exhibited clinical signs of myositis. The elevations in liver enzymes and CPK were not considered to be clinically significant. On any particular visit, the number of laboratory values out of the normal range never exceeded 20.

Only 1 patient showed an adverse change on ophthalmologic examination: a posterior subcapsular opacity in both eyes just visible at 6-month examination. By the end of the study, 32 patients exhibited minor ophthalmologic changes observed in the slit-lamp examination. These changes were considered unrelated to the study drug.

Because the study was uncontrolled, it is difficult to evaluate the results of these ophthalmologic findings compared with those in a similar untreated patient population.

DISCUSSION

The results of this study confirmed the well-established efficacy of the HMG CoA reductase inhibitor lovastatin in improving the blood lipid profile. It also extends the beneficial findings to women, the elderly, and hypertensive patients taking antihypertensive therapy, which can unfavorably alter blood lipids.

The demonstration of efficacy in the elderly is important because patients in this group have a high absolute risk of CAD. The demonstration of the high efficacy in hypertensive patients has relevance because hypertensive patients have a greater than average prevalence of blood lipid abnormalities.[7] Also, it had not been possible to show any benefit of antihypertensive therapy against CAD in the presence of raised serum cholesterol.[8] The demonstration of equal efficacy of lovastatin in hypertensive and normotensive patients may have relevance in the management of patients with hypertension and hypercholesterolemia.

Following the National Cholesterol Education Program Guidelines[7] will require that a significant number of patients be treated with drugs that are effective and well tolerated. Optimal therapy requires that LDL cholesterol be lowered, HDL cholesterol raised, and total/HDL cholesterol reduced.[9] In the present study, lovastatin appeared to fulfill this requirement. Furthermore, it appeared to be usually well tolerated. Its effectiveness in actually reducing CAD events and in retarding angiographically measured atherogenesis is under investigation.

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Extended Clinical Safety Profile of Lovastatin

Geraldine Mantell, MD, M. Theresa Burke, MD, and Joan Staggers, PhD

Lovastatin has been available for prescription use in the United States for about 20 months (as of June 1989). Over 1 million patients have received the prescription drug, and approximately 14,000 patients have participated in clinical trials. It is estimated that 500,000 patients have received lovastatin continuously for at least 1 year. This report reviews the extended safety experience from all clinical trials and prescription use.

At least 645 patients have received lovastatin for more than 3 years. There are new data from a recently completed 1 year, placebo-controlled trial in 8,245 patients (Expanded Clinical Evaluation of Lovastatin study) and 20 months of health professionals' reports on spontaneous adverse events associated with large prescription usage. Data from recent large clinical trials suggest that the risk of myopathy and asymptomatic sustained liver transaminase elevations is less than reported in prior studies. The early clinical trials enrolled very high risk patients receiving lovastatin at a usual dose of 80 mg/day and often receiving concomitant hypolipidemic agents including gemfibrozil and niacin. After more than 42 months' long-term clinical trial experience, data have not established adverse effects from lovastatin on the human lens.

Possible new types of rare drug-related adverse events observed with large prescription use include hypersensitivity reactions such as arthralgia, thrombocytopenia, symptomatic hepatitis and interaction with warfarin.

No new, unique adverse-event profile has emerged with extended clinical use, including use in a few patients who have received therapy for more than 5 years. The lovastatin extended safety profile is that of a generally well-tolerated drug.

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Lovastatin is the first approved drug in a new class of hypolipidemic agents, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. Its mechanism of action is to partially inhibit an early step in cholesterol synthesis, yet permit enough mevalonate to be synthesized so that there is adequate cholesterol for cell membrane function and steroidogenesis.[1] There is no interference in the late cholesterol pathway and thus no buildup of toxic metabolites such as occurred with triparanol (MER-29).[2] The drug appears to be well tolerated and has potent cholesterol-lowering efficacy. Its principal effect is to reduce low-density lipoprotein cholesterol, which is considered to be the most atherogenic factor in the atherosclerotic process. It also modestly increases high-density lipoprotein cholesterol. At the full therapeutic dose (80 mg/day), lovastatin decreases low-density lipoprotein cholesterol levels 41% and increases high-density lipoprotein cholesterol levels 9 to 10%.[3] Lovastatin has been available for prescription use for 20 months (June 1989). This report reviews the safety profile available as of June 1989. This information is from clinical trials and spontaneous adverse experiences reported to Merck Sharp & Dohme Research Laboratories. In the 20 months since the drug was introduced, approximately 1 million patients have received lovastatin by prescription, and approximately 500,000 of these patients have received therapy for at least 1 year. Additionally, approximately 14,000 patients have participated in clinical trials.

Reports on spontaneous adverse experiences are regularly reviewed by an internal safety committee at Merck Sharp & Dohme Research Laboratories. The pattern of adverse experiences and the frequency of reports associated with prescription use are monitored on a continuous basis. The data base from the ongoing review was summarized after approximately 9 and 17 months of prescription experience, when the total patient exposure was approximately 400,000 and 850,000, respectively. In addition, the frequency of the described adverse events was monitored further on a monthly basis until June 30, 1989, to detect any increase in frequency of the reported adverse events or any new types of reported adverse events.

The clinically important adverse experiences continue to be increases in liver transaminases and, though rare, myopathy or rhabdomyolysis, or both. No evidence of an effect on the human lens is apparent to date from clinical trials or prescription use. Finally, rare, possibly drug-related new adverse events, not seen in clinical trials, are identified. It is usually impossible to see rare adverse events in clinical trials because the number of patients receiving the drug is small compared with the number involved in prescription use.

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TABLE I Sustained Transaminase Elevations (More Than Three Times Upper Limit of Normal) Seen in 8,245-Patient, Placebo-Controlled, Multicenter EXCEL Study—Preliminary Data

Treatment	Cases	Comments* (no. of pts.)
Placebo	2	None
20 mg/day	2	Primary biliary cirrhosis (1)
20 mg bid	11	Viral hepatitis (2)
40 mg/day	12	Gallstones (1) Hepatitis A (1) Septicemia (1)
40 mg/bid	20	None
Total	47	

* Other conditions diagnosed that probably accounted for the enzyme elevations.

REPORTS ON ADVERSE EXPERIENCES FROM CLINICAL TRIALS

Long-term safety data: The original registration document included a cohort of 744 patients of whom approximately 650 have been followed for more than 3 years. The safety data for this patient population were summarized and first published in November 1988.[4] Drug-attributable adverse events that caused patients to be withdrawn from this study before March 1988, the cutoff date for the first published summary, include clinically important asymptomatic transaminase elevations (1.3%), rash (0.3%), gastrointestinal symptoms (0.3%), myopathy (0.1%) and insomnia (0.1%).

In this ongoing study, patients have now completed more than 3 years of treatment as of June 1989 and will be followed for a total of 5 years. Only 2 additional drug-related adverse experiences have been reported since March 1988 that have resulted in withdrawal of patients from the study.[5] One case of rash occurred, and 1 patient had sustained elevations in levels of transaminases (levels >3 × the upper limit of normal), which occurred after previous low-grade transaminase elevations in the first year of treatment. No additional cases of myopathy have been reported and no unique, new, adverse experience profile has emerged with long-term use of the drug.[5] No additional patients had therapy discontinued because of gastrointestinal symptoms or insomnia.

The prevalence of lens opacities for the cohort of 454 patients from phase III trials after a mean of 19 months of lovastatin treatment increased 1.2%. The expected age-related increase in prevalence of lens opacities is approximately 2.5% for this time interval.[4] These findings and an observer reliability study suggest that there is a great deal of intraobserver and interobserver variability in the slit-lamp examination.[6,7] Eight patients underwent cataract surgery, 6 of whom had definite opacities at baseline. All 8 patients were older than 60 years, an age when the prevalence of cataracts is high.[5]

The preliminary results of an 8,245-patient, placebo-controlled, 48-week study (Expanded Clinical Evaluation of Lovastatin [EXCEL]), which is described elsewhere in this supplement, show no evidence of an effect of lovastatin on the human lens.[6] Additionally, a sophisticated placebo-controlled, 2-year ophthalmologic study utilizing Scheimpflug and Neitz retroillumination photography is ongoing to add additional evidence that lovastatin has no effect on the human lens.[8] At this time, it is still recommended that slit-lamp examination be performed before starting treatment and at annual intervals thereafter.

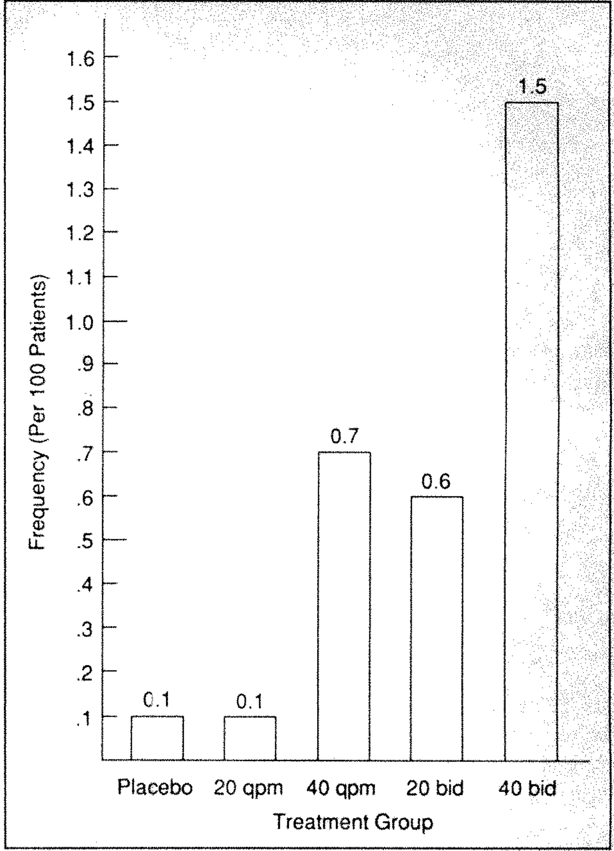

FIGURE 1. Percent of randomized patients withdrawn from treatment for sustained transaminase elevations.

Expanded Clinical Evaluation of Lovatatin study: Merck Sharp & Dohme Research Laboratories conducted a large, placebo-controlled, 362-site, double-blind trial in which 8,245 patients with total cholesterol levels between 240 and 300 mg/dl (low-density lipoprotein cholesterol >160 mg/dl) who were receiving a lipid-lowering diet were randomized to treatment for 48 weeks.[9] Four therapeutic doses of lovastatin ranging from 20 mg with the evening meal to 40 mg twice daily were compared with placebo. Approximately 6,400 patients were randomized to receive lovastatin and 1,600 to matching placebo. This study was completed in July 1989. The baseline characteristics of the patient population are presented elsewhere in this supplement and preliminary results have recently been presented.[9,10] Complete reports of final results will be available in 1990. The 3 principal areas of safety concern with regard to lovastatin are the liver, muscle and lens; therefore, preliminary data obtained from the study concerning these organs will be presented as part of the extended safety profile for lovastatin.

Sustained liver transaminase elevations from the preliminary unblinded data for the patients withdrawn from the study before completion in July 1989 are listed in Table I. A sustained transaminase elevation is defined as a level that is more than 3 × the upper limit of normal on 2 repeat tests performed approximately 1 week apart. The estimated percentage of patients from this study with a sustained elevation in either alanine or aspartate aminotransferase levels, or both, is presented in Figure 1. The incidence of clinically important asymptomatic transaminase elevations in this 8,245-patient study was substantially lower than the incidence reported in the organized clinical trials (0.6 vs 1.9%, respectively). Most of the patients in the original clinical trials had plasma cholesterol levels well in excess of 300 mg/dl even though they were receiving a lipid-lowering diet and were receiving the maximal therapeutic dose, 80 mg/day. The preliminary distribution of sustained transaminase elevations in this large placebo-controlled study suggests a possible dose relation that is consistent with a mechanism-based effect. Only 1 patient who received 20 mg/day had clinically important liver transaminase elevations that were considered to be probably drug-related. In another patient in the lovastatin 20 mg group, a liver biopsy spepcimen showed primary biliary cirrhosis; in retrospect, serum alkaline phosphatase levels were elevated before treatment in this patient.

All patients with sustained transaminase elevations who were withdrawn from this multicenter trial were asymptomatic, and their transaminase levels returned to normal values, usually within a few days to several weeks after therapy was discontinued. A few patients, however, continued to receive lovastatin therapy; elevated transaminase levels also returned to values within normal limits in this group. However, at this time it is recommended that liver enzymes be monitored before starting treatment and every 4 to 6 weeks during the first 15 months and periodically thereafter in all patients.

In this study, serum creatine phosphokinase elevations were routinely monitored to determine the incidence of marked elevations and any clinical symptomatology associated with the elevations. A marked elevation was arbitrarily defined as a level >1,000 U/liter (5 × the upper limit of normal). The blinded data for patients with serum creatine phosphokinase levels >1,000 U/liter are listed in Table II; in these patients, only 1 definite case of myopathy was reported, in a patient who received lovastatin 40 mg twice daily. This patient had acute cholecystitis at the time of the clinical diagnosis of myopathy, and there may have been a common duct stone that interfered with biliary flow. Three other cases were reported in which the diagnosis was not clear and may represent either myalgia or myopathy. Two of these patients continued in the study without further symptoms. No patient in this study developed rhabdomyolysis. Rhabdomyolysis is characterized by muscle symptoms, myoglobinuria or acute renal failure, or a combination. Lovastatin was used as the only hypolipidemic agent in this trial in patients receiving a lipid-lowering diet who had total cholesterol levels between 240 and 300 mg/dl. Virtually none of the patients in this placebo-controlled large study was receiving cyclosporine therapy or concomitant gemfibrozil or niacin.

TABLE II CPK Elevations (>1,000 U/l) on Two Occasions Approximately One Week Apart—Preliminary Data from the EXCEL Study

	Cases	Estimated Incidence Through Week 48 (%)
Single elevations	107	1.5
Sustained elevations	11*	0.1

* Seven patients were withdrawn because of sustained elevations; 5 patients had vague muscle aches, and 1 patient had definite myopathy.
CPK = creatine phosphokinase.

Most hypercholesterolemia in the United States population occurs at levels between 240 and 300 mg/dl. Persons with hypercholesterolemia in this range should be considered for drug therapy after an adequate trial of lipid-lowering diet fails to meet the desired goal currently recommended for optimal plasma cholesterol, i.e., 200 mg/dl.[11] The primary data from the 8,245-patient multicenter trial (EXCEL study) would suggest that such patients receiving lovastatin as the only hypolipidemic drug and not receiving concomitant immunosuppressive therapy are at less risk for myopathy than the high-risk patients enrolled in the original clinical trials. These patients had a mean plasma cholesterol level of 359 mg/dl.

Lens examinations were performed in the EXCEL trial using a new classification system for describing lens findings.[7] The first 1,441 patients were analyzed in a blinded fashion after 6 months of treatment, and recorded changes were within the range of previously reported reliability,[7,10] indicating the absence of a substantial shift in the distribution of lens findings. The examinations were done by the same observer in approximately 90% of patients. This is further evidence to suggest that lovastatin has not been established to have an effect on the human lens.

COMPARISON OF TYPES OF SPONTANEOUS ADVERSE EXPERIENCES REPORTED FROM PRESCRIPTION USE AND CLINICAL TRIALS

Although it is not possible to estimate accurately the rate of spontaneous adverse experience reported from prescription use, the pattern of adverse experiences seen with prescription use can be compared with that seen in clinical trials. Spontaneous reporting is influenced by many factors including length of time since introduction of the drug, amount of physician awareness and use of the drug, and the seriousness of the adverse experience. A comparison of the distribution patterns from spontaneous reporting and from clinical trials suggests that the types of adverse events from both sources are similar.

Few new types of adverse experiences have been reported. The new adverse experiences include hypersensitivity reactions, symptomatic hepatitis, arthralgia, thrombocytopenia and possibly interaction with warfa-

TABLE III Cases of Rhabdomyolysis with Lovastatin: Postmarketing Reporting as of March 1989

		Gender		Lovastatin				Outcome[*]	
Total Cases	Age (yr)	M	F	Dose (mg)	Time/Onset	Suspect Concomitant Medications	No. of Pts.	Recovered	Died
24	33–79	11	10	20–80	4 days/8 mo	Gemfibrozil	10	20	1[†]
		NA = 3				Niacin	3[‡]	NA = 3	
						Cyclosporine	2[‡]		
						Erythromycin	2		
						None	3		
						Unknown	5		

[*] Outcome reflects the patient's status as of the last report received.
[†] Patient refused dialysis.
[‡] One patient was receiving both niacin and cyclosporine concomitantly with lovastatin.
NA = Not available.

rin. These are rare events, as they were not reported in the original clinical trials, which enrolled a smaller number of patients. This is not unexpected as rare events usually become apparent only when large numbers of patients receive the drug such as has occurred in the extensive prescription use of lovastatin.

HIGHLIGHTS OF SPONTANEOUS ADVERSE EXPERIENCE REPORTS FOR LIVER, MUSCLE AND LENS

The liver: The cause of each reported adverse event considered serious according to the Food and Drug Administration reporting criteria cannot be determined unless a rechallenge is done. Pretreatment information was often not included. The 49 cases of adverse experiences affecting the liver that were considered serious were submitted to an outside hepatologist (W. E. Maddrey, MD) for evaluation. Eight to 21 of the cases were considered to be possibly or probably drug-related depending on the reviewer; none was considered to be definitely drug-related. Follow-up was obtained in all but 1 of the cases believed to be possibly or probably drug-related. All had recovered or were recovering. There were reports of 2 positive rechallenges (increase in levels of liver transaminases on reinstitution of lovastatin). With few exceptions, the primary abnormality was hepatocellular. Liver biopsy was performed in 7 patients and usually showed fatty changes. Four reports included a cholestatic component.

Two deaths related to liver disease were reported, both of which were not considered to be drug-related. One of the patients with apparent cholestatic hepatitis died suddenly. The cause of death at autopsy was thought to be arteriosclerotic heart disease. There was 1 report of liver necrosis in a patient with preexisting polycystic kidney disease who had been maintained on dialysis. The patient had a history of multiple blood transfusions and developed hypotension and sepsis. The attending physician believed that these factors were responsible for the adverse outcome.

We continue to evaluate the reports of hepatic adverse experiences as part of our overall lovastatin postmarketing surveillance. As of the end of June 1989, there was no increased frequency in reporting. "Hepatitis" and "cholestatic jaundice" have been added to the list of causally related adverse experiences in the package circular. "Hepatitis" is defined as clinically symptomatic transaminase elevation(s), in contrast to the usual asymptomatic elevations already known to occur with lovastatin therapy from clinical trial experience. The 4 reports on "cholestatic jaundice" showed a mixed cellular-biliary obstruction pattern and included elevated bilirubin and alkaline phosphatase levels as well as increases in transaminase levels. Both of these adverse experiences (hepatitis, cholestatic jaundice) appear to be rare, judging by the small number of spontaneous reports received. In addition, no such event was reported from the 8,245-patient, placebo-controlled EXCEL study.

Muscle: Seventeen reports of myopathy or myositis that were considered serious were received at Merck, Sharp & Dohme Research Laboratories by March 1, 1989. Twenty-four cases of rhabdomyolysis, all serious, were reported in the same time period. The patients were usually taking concomitant gemfibrozil, niacin or immunosuppressive therapy, or a combination. Sepsis was present in 2 cases. Although erythromycin was concomitant therapy in 2 reports, 2 additional reports in which different antibiotics were given as concomitant therapy have recently been received. Both additional patients had severe infections which may be the common factor in the 4 antibiotic-associated cases that have been reported. The demographics for the 24 patients with rhabdomyolysis are listed in Table III. This apparently rare adverse event has not increased in frequency as of June 1989.

Lens: Fifty-four spontaneous reports describing lens opacities or cataracts, or both, observed after initiating lovastatin therapy, were received as of March 1989. The details were usually incomplete. Pretreatment examination and the location of the opacity were not always reported. This number of reports is not large, given that the mean age of the population receiving the drug is >60 years, that a large number of patients received the drug and that the current label recommendation is to perform an annual slit-lamp examination. Furthermore, other studies (Laties et al, unpublished data, 1990) show that there is a high prevalence of lens opacities in this age group. Even with a doubling of prescription use, the frequency of reported lens opacities has not changed in the period covered. The information from prescription use for 20 months (as of June 1989) continues to show that no causal relation has been established of an effect of lovastatin on the human lens.[6]

REPORTS OF SPONTANEOUS ADVERSE EXPERIENCES OF CLINICAL IMPORTANCE NOT REPORTED IN CLINICAL TRIALS

As of March 1989, 25 spontaneous reports have described serious, possibly drug-related hypersensitivity reactions.[5] Included are 1 to a few reports each of angioneurotic edema, urticaria, arthritis, arthralgia, antinuclear-antibody-positive lupus-like syndrome, polymyalgia rheumatica, leukopenia, thrombocytopenia and asthenia/fatigue. Causal relation has not been established in all reported cases. As with most drugs, hypersensitivity response to lovastatin appears to be a very rare adverse event.

Ten cases of a possible lovastatin-warfarin interaction have been reported.[5] Although not noted in clinical trials, precautionary information is now in the package circular.

Overall, few new types of adverse experiences that differ from the adverse-experience profile seen in clinical trials have occurred in spontaneous adverse experience reporting to Merck Sharp & Dohme. Generally, these new types of events appear to occur only rarely.

DISCUSSION

Lovastatin has received wide acceptance by the medical community and by patients with hypercholesterolemia. After 20 months of prescription use, more than 1 million patients have received the drug as of June 1989. Furthermore, approximately 500,000 patients have been taking the drug for at least 1 year. The generally good safety profile demonstrated in clinical trials is also seen in more extended use. Approximately 650 patients have received the drug for more than 3 years, and a few patients have received the drug for more than 5 years.[12] Approximately 6,400 patients received lovastatin in recommended therapeutic dosages in the placebo-controlled, multicenter EXCEL trial completed in July 1989.

This safety profile overview of lovastatin describes the adverse experience profile from clinical trials and spontaneous reporting. Few new adverse experiences have become apparent from large prescription experience that differ from those observed in clinical trials. The most noteworthy adverse experiences continue to be asymptomatic liver transaminase elevations (reversible on discontinuation of treatment) that are apparently dose-related and possibly mechanism-based, and myopathy, though rare, or the more serious rhabdomyolysis. Hepatitis and cholestatic jaundice have also been rarely reported from prescription use but were not seen in the clinical trials conducted to date.

Preliminary data from a large, placebo-controlled clinical trial (EXCEL) show that lovastatin, administered as the sole hypolipidemic agent and without immunosuppressive therapy to patients with moderate hypercholesterolemia (240 to 300 mg/dl), has a good safety profile. The incidence of sustained transaminase elevations (>3 times the upper limit of normal) is less than that cited in earlier studies and appears to be dose-related and possibly mechanism-based. Myopathy, when the drug is used alone, is rare, with only 1 definite case reported in the large 8,245-patient EXCEL study. The patients reported with rhabdomyolysis from postmarketing experience have usually been taking concomitant treatment that included gemfibrozil, immunosuppressive therapy, niacin and/or have had serious infections.

Evidence from clinical trials to date, with a few patients receiving lovastatin for more than 5 years, demonstrates no effect of lovastatin on the human lens.[12] Several controlled clinical trials indicate that hypercholesterolemic patients have a high incidence of lens opacities at baseline and that no unexpected increase in incidence occurs with prolonged use of the drug beyond what would be expected with the increasing age of the patient.[4,5]

CONCLUSIONS

Lovastatin is generally well tolerated. A treatment that is easy to take and well tolerated has not been available previously to manage patients with hypercholesterolemia. Lovastatin is an effective lipid-lowering agent.

Extended clinical experience with lovastatin is now becoming available. The benefit-to-risk ratio continues to be favorable.

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Comparison of the Effects of Lovastatin and Gemfibrozil on Lipids and Glucose Control in Non-Insulin-Dependent Diabetes Mellitus

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Patients with non-insulin-dependent diabetes mellitus have an increased incidence of coronary artery disease which may, in part, be associated with abnormalities in plasma lipids. In a double-blind, parallel, randomized study, lovastatin and gemfibrozil were compared in 102 diabetic patients with primary hypercholesterolemia; two-thirds of the patients were treated with oral hypoglycemic agents and one-third received diet therapy alone for their diabetes. Mean pretreatment total and low-density lipoprotein (LDL) cholesterol values were 273 and 193 mg/dl, respectively. Lovastatin significantly reduced total, LDL and very low density lipoprotein cholesterol (20, 26 and 28%, respectively) and raised high-density lipoprotein (HDL) cholesterol (14%). Gemfibrozil significantly reduced triglycerides and very low density lipoprotein cholesterol (36 and 41%, respectively) and, to a lesser extent, total cholesterol (9%); it also increased HDL cholesterol (21%). Lovastatin therapy was not associated with a significant change in triglycerides, and gemfibrozil did not significantly lower LDL cholesterol. The decrease in the ratio of total to HDL cholesterol tended to be greater with lovastatin than with gemfibrozil (26.5 and 20.4%, respectively; $p = 0.053$). Changes in lipid profiles with both agents were of a degree similar to those reported in nondiabetic patients. Neither agent had a clinically important effect on fasting glucose or hemoglobin A_{1c}. Both drugs were well tolerated with the exception of 2 patients treated with gemfibrozil who developed symptoms of cholecystitis.

(Am J Cardiol 1990;66:16B–21B)

There is an increased prevalence of elevated triglyceride and depressed high-density lipoprotein (HDL) cholesterol levels in patients with non-insulin-dependent diabetes mellitus (NIDDM).[1-4] Although low-density lipoprotein (LDL) cholesterol levels are less affected by NIDDM, alterations have been demonstrated in LDL particle composition that render these particles possibly more atherogenic.[5-7] Thus, the contribution of lipid disorders to the development of atherosclerosis in NIDDM may be enhanced by the effect of the diabetic state on lipoproteins in addition to abnormalities in circulating levels of lipoproteins.[8] It is therefore especially important for these patients to maintain a desirable lipid profile. Failure to achieve desirable plasma lipid levels through glycemic control and dietary modification is an indication for the use of lipid-lowering agents in these high-risk subjects.[9]

Bile sequestrants and niacin are recommended for the treatment of hypercholesterolemia. However, the sequestrants commonly cause constipation and tend to increase triglyceride levels,[10] which may already be elevated in patients with diabetes, and niacin may aggravate glucose intolerance.[11] Alternative forms of drug therapy are therefore needed. Lovastatin, the first marketed 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor, has been shown in nondiabetic subjects to be an effective and well-tolerated drug for the treatment of primary hypercholesterolemia.[12-14] Several short-term studies have demonstrated similar properties of this agent in patients with NIDDM without any evidence of effects on glycemic control.[15-16]

To further evaluate the utility of lovastatin in the treatment of primary hypercholesterolemia in subjects with NIDDM, we have conducted a 24-week double-blind, multicenter trial of lovastatin compared with the fibric-acid derivative gemfibrozil. Gemfibrozil has triglyceride-lowering and mild cholesterol-lowering properties and may rarely aggravate glucose intolerance.[17]

METHODS

Patients with primary hypercholesterolemia and NIDDM controlled by diet alone or by oral hypoglycemic agents were counseled in the American Heart Association Phase I diet. After 4 weeks on the diet, patients were entered into an 8-week double placebo baseline period after giving written informed consent. One hundred and four patients aged 18 to 70 years at 11 sites met study criteria during the placebo baseline period and were randomized. Both LDL cholesterol levels at the beginning

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and after 6 weeks of placebo were required to be at least 160 mg/dl if, in addition to diabetes, another risk factor described in the National Cholesterol Education Program Guidelines was present[9]; if no other risk factor was present, both LDL cholesterol levels were required to be at least 190 mg/dl. The LDL cholesterol levels at the beginning and after 6 weeks of placebo were also required to be within 10% of each other. Serum glucose levels on the same 2 occasions were each less than 200 mg/dl and averaged less than 180 mg/dl. Triglyceride levels were below 400 mg/dl, and there was no other secondary cause of hyperlipidemia such as nephrotic syndrome or insufficiently treated thyroid disease. There was no evidence of clinically significant hepatic or renal disease and no history of gallbladder disease. Concurrent treatment with other lipid-lowering agents was not permitted at any time during the study. Other chronic therapy such as antianginal or antihypertensive treatment was permitted if the dosage was constant.

Patients were randomized to double-blind therapy of lovastatin, 20 mg, with the evening meal or gemfibrozil, 300-mg capsules, 2 with the morning and 2 with the evening meal. All patients received placebo for the alternate therapy. Therapy continued for 24 weeks with follow-up visits every 6 weeks. If the LDL cholesterol level remained higher than 160 mg/dl after 6 weeks of therapy, the dose of lovastatin or its matching placebo was increased to 40 mg with the evening meal (two 20-mg tablets). There was no change in the dose of gemfibrozil or its matching placebo.

Patients presented to the clinic for each visit after a 12- to 14-hour fast and had blood samples obtained for measurement of lipid levels and routine testing for safety monitoring. Total and HDL cholesterol and triglycerides were measured by standard techniques,[18-20] while very low density lipoprotein (VLDL) cholesterol and LDL cholesterol were calculated.[21] At the randomization and 24-week visits, additional blood was obtained for determination of VLDL cholesterol after isolation of VLDL by ultracentrifugation. The specimens were analyzed by SmithKline Bioscience Laboratories, Van Nuys, California. During the baseline period and at the end of the study, physical examination and electrocardiography were performed, and patients were examined by an ophthalmologist with special attention paid to the examination of the lens. Diet counseling was repeated, and diets were periodically monitored by a dietitian throughout the study.

In the statistical analysis, percentage changes from baseline of lipid variables, glucose and hemoglobin A_{1c} (HbA_{1c}) were evaluated using an intent-to-treat approach. Thus, if data from a particular visit were missing, data were carried forward from the previous visit, as long as data from at least 1 visit during the treatment period were available. Comparisons between groups were made using a general linear model appropriate for unbalanced analysis of variance with model factors of treatment group (fixed effect), investigator (random effect) and their interaction (random effect). The effect of age and gender on the response to treatment was not considered for this initial analysis. When no significant ($p < 0.10$) interactions were found, a main-effects model was fitted using Henderson's method[22] of fitting constants (Statistical Analysis System, Cary, North Carolina [SAS] software package type II sums of squares). If the interaction was significant, Yates squares of means (SAS type III sums of squares) was used to fit the model. For categoric data, the comparisons between treatment groups were made using the Fisher exact test. The Wilcoxon's signed-rank test was employed for within-group comparisons. All tests were performed at $\alpha = 0.05$ (2-tailed). P values >0.05 but <0.10 were also noted. P values ≥0.10 were noted as not significant.

TABLE I Baseline Characteristics

	Lovastatin	Gemfibrozil
No. of pts.[*]	50	52[†]
Sex (male/female)	23/27	20/32
Age (range in years)	32–88	39–73
Oral agent [n(%)]	35 (70%)[‡]	37 (71%)
Diet (n[%])	15 (30%)	15 (29%)
Fasting blood sugar (mg/dl)	170 ± 44	153 ± 41
Hemoglobin A_{1c} (% of total)	6.6 ± 1.3	6.1 ± 1.4
(normal 3.6–6.1%)	(n = 50)	(n = 49)[§]
Total cholesterol (mg/dl)	272 ± 36	274 ± 34
	(n = 50)	(n = 51)
LDL cholesterol (mg/dl)	189 ± 35	189 ± 30
(Friedewald, TG < 400 mg/dl)	(n = 46)	(n = 47)
LDL cholesterol (mg/dl)[‖]	194.0 ± 31.9	192.0 ± 30.8
(with VLDL by ultracentrifugation)	(n = 42)	(n = 38)
<190 mg/dl (n[%])	24 (53%)	22 (54%)
≥190 mg/dl (n[%])	21 (47%)	19 (46%)
TG (mg/dl)	202 ± 114	218 ± 124
	(n = 50)	(n = 51)
HDL cholesterol (mg/dl)	42 ± 10	42 ± 10
	(n = 50)	(n = 51)
VLDL cholesterol (mg/dl)[‖]	36.1 ± 21.4	39.6 ± 25.3
(ultracentrifugation)	(n = 42)	(n = 38)

[*] Two additional patients entered but had no efficacy data and are excluded from analyses.

[†] Lipid values from 1 patient who developed severe hypertriglyceridemia during gemfibrozil treatment are excluded from mean lipid values.

[‡] Number (percent) or mean ± standard deviation, as noted.

[§] Three patients with variant hemoglobins are excluded.

[‖] VLDL by ultracentrifugation was not available for some patients.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides; VLDL = very low density lipoprotein.

RESULTS

Of 104 patients entered, 102 met entry criteria and had data from at least 1 visit after randomization available for analysis. Fifty patients were randomized to lovastatin and 52 to gemfibrozil therapy. Forty-five patients taking lovastatin and 48 patients taking gemfibrozil completed 24 weeks of therapy. The 2 groups were similar at randomization; baseline characteristics are listed in Table I. The lipid values before and at the end of treatment and the percent changes are listed in Table II. One patient treated with gemfibrozil gained 40 pounds and developed severe hypertriglyceridemia (triglycerides 4,170 mg/dl, total cholesterol 594 mg/dl, VLDL cholesterol by ultracentrifugation 296 mg/dl and HDL cholesterol 29 mg/dl) and was excluded from lipid analyses; overall conclusions, however, were not changed when this patient was included in the analyses. Thus, data were available on 50

TABLE II Lipid Values

	Treatment	No. of Pts.*	Baseline Mean	SD	Week 24 Mean	Week 24 SD	Change % Mean	Change % SD	p Value (from Baseline)	p Value (Between Groups)
LDL cholesterol (mg/dl)	Lovastatin	42	194.0	31.9	141.7	28.5	−26.2	13.2	<0.01	<0.01
	Gemfibrozil	38	192.0	30.8	188.3	38.8	−1.1	17.7	NS	
Total cholesterol (mg/dl)	Lovastatin	50	271.9	36.1	216.7	38.0	−20.0	12.0	<0.01	<0.01
	Gemfibrozil	51	274.3	34.3	255.2	47.4	−6.8	14.2	<0.01	
HDL cholesterol (mg/dl)	Lovastatin	50	42.1	9.8	47.2	13.7	13.6	33.3	<0.01	NS
	Gemfibrozil	51	41.8	9.7	49.5	11.8	21.3	31.9	<0.01	
VLDL cholesterol ultracentrifugation (mg/dl)	Lovastatin	42	36.1	21.4	24.9	18.5	−27.9	43.0	<0.01	NS
	Gemfibrozil	38	39.6	25.3	21.1	16.0	−41.1	34.1	<0.01	
Triglycerides (mg/dl)	Lovastatin	50	202.3	114.4	190.2	119.0	1.8	58.9	NS	<0.05
	Gemfibrozil	51	217.2	125.5	129.0	57.4	−36.0	24.6	<0.01	
TC/HDL ratio	Lovastatin	50	6.8	1.8	4.9	1.5	−26.5	16.5	<0.01	=0.053
	Gemfibrozil	51	6.9	1.5	5.4	1.4	−20.4	15.6	<0.01	

* One patient was excluded because of triglycerides >4,000 mg/dl during gemfibrozil treatment.
NS = not significant; SD = standard deviation; TC/HDL ratio = the ratio of total cholesterol to high-density cholesterol; other abbreviations as in Table 1.

patients treated with lovastatin and 51 treated with gemfibrozil. Measured VLDL cholesterol values (done at baseline and at week 24) and the LDL cholesterol results calculated from these data were available for 42 patients treated with lovastatin and 38 patients treated with gemfibrozil.

Both drugs significantly lowered total cholesterol levels ($p < 0.01$). Lovastatin, but not gemfibrozil, significantly lowered LDL cholesterol levels ($p < 0.01$). The decreases in mean total and LDL cholesterol in the lovastatin group (20 and 26%, respectively) were significantly greater ($p < 0.01$) than those in the gemfibrozil group (7 and 1%, respectively). Twenty-one patients treated with lovastatin and 19 patients treated with gemfibrozil had LDL cholesterol levels at randomization ≥ 190 mg/dl; in 18 patients in the lovastatin group and in 16 patients in the gemfibrozil group, treatment as well as baseline values were available. Among these 34 patients, significantly more patients treated with lovastatin (72%) had final LDL cholesterol levels <160 mg/dl compared with patients treated with gemfibrozil (19%) ($p < 0.01$). Similarly, within this subgroup, more patients treated with lovastatin had $\geq 20\%$ reduction in LDL cholesterol than patients treated with gemfibrozil (94 vs 25%, respectively) ($p < 0.01$). After 6 weeks of therapy, LDL cholesterol was calculated using the Friedewald equation[21] (LDL cholesterol = total cholesterol − HDL cholesterol − triglycerides ÷ 5) since VLDL cholesterol was not measured using ultracentrifugation at this visit. Half the patients treated with lovastatin, 20 mg once daily, had LDL cholesterol values that were <160 mg/dl and, therefore, did not require titration to 40 mg once daily. This is significantly greater ($p < 0.01$) than the 15% of patients treated with gemfibrozil, 600 mg twice daily, who had LDL cholesterol values <160 mg/dl and did not require titration of the placebo matching lovastatin.

Both drugs increased HDL cholesterol levels ($p < 0.01$). There was no significant difference in the effect

TABLE III Lipid Values in Diet-Controlled Diabetics

	Treatment	No. of Pts.*	Baseline Mean	SD	Week 24 Mean	Week 24 SD	Change % Mean	Change % SD	p Value (from Baseline)	p Value (Between Groups)
LDL cholesterol (mg/dl)	Lovastatin	9	174.8	34.4	138.7	22.6	−20.0	7.9	<0.01	NS
	Gemfibrozil	10	186.2	23.9	183.0	30.4	−0.8	24.4	NS	
Total cholesterol (mg/dl)	Lovastatin	15	270.1	42.9	224.5	39.8	−16.5	12.0	<0.01	= 0.05
	Gemfibrozil	14	260.7	26.0	254.1	43.3	−2.1	16.2	NS	
HDL cholesterol (mg/dl)	Lovastatin	15	40.5	12.1	50.5	18.7	29.7	55.4	<0.01	NS
	Gemfibrozil	14	39.4	10.6	52.6	13.5	41.2	50.4	<0.01	
VLDL cholesterol ultracentrifugation (mg/dl)	Lovastatin	9	53.4	28.0	28.7	19.3	−40.8	39.9	<0.05	= 0.052
	Gemfibrozil	10	32.9	24.3	20.7	20.4	−31.3	45.6	= 0.08	
Triglycerides (mg/dl)	Lovastatin	15	230.9	139.0	181.6	103.8	−12.0	37.9	NS	NS
	Gemfibrozil	14	194.4	81.4	119.4	61.5	−34.8	26.9	<0.01	
TC/HDL ratio	Lovastatin	15	7.2	2.4	4.9	1.7	−28.9	20.2	<0.01	<0.05
	Gemfibrozil	14	7.0	1.8	5.1	1.3	−25.6	18.3	<0.01	

* One patient was excluded because of triglycerides >4,000 mg/dl during gemfibrozil treatment.
Abbreviations as in Tables I and II.

TABLE IV Lipid Values in Patients Taking Oral Hypoglycemic Agents

	Treatment	No. of Pts.	Baseline Mean	SD	Week 24 Mean	Week 24 SD	Change % Mean	Change % SD	p Value (from Baseline)	p Value (Between Groups)
LDL cholesterol (mg/dl)	Lovastatin	30	200.0	30.9	142.1	30.8	−28.4	14.1	<0.01	<0.01
	Gemfibrozil	26	193.0	32.1	186.7	40.5	−3.1	14.6	NS	
Total cholesterol (mg/dl)	Lovastatin	35	272.7	33.4	214.2	37.9	−21.5	12.2	<0.01	<0.01
	Gemfibrozil	37	279.6	35.9	254.6	48.6	−8.9	13.2	<0.01	
HDL cholesterol (mg/dl)	Lovastatin	35	42.8	8.8	46.1	11.6	7.4	13.9	<0.01	= 0.095
	Gemfibrozil	37	42.7	9.4	48.2	11.0	13.8	16.8	<0.01	
VLDL cholesterol ultracentrifugation (mg/dl)	Lovastatin	30	31.4	17.5	23.5	18.0	−25.0	42.2	<0.01	<0.05
	Gemfibrozil	28	42.0	25.8	20.8	14.8	−46.3	28.9	<0.01	
Triglycerides (mg/dl)	Lovastatin	35	190.1	102.0	195.5	126.6	9.6	67.3	NS	<0.01
	Gemfibrozil	37	225.8	138.6	134.9	71.6	−35.2	25.6	<0.01	
TC/HDL ratio	Lovastatin	35	6.6	1.4	4.9	1.5	−25.3	16.0	<0.01	<0.05
	Gemfibrozil	37	6.8	1.4	5.5	1.5	−18.7	13.9	<0.01	

Abbreviations as in Tables I and II.

of the 2 drugs on HDL cholesterol levels. Although both drugs decreased the total/HDL cholesterol ratio, the decrease tended to be greater with lovastatin (p = 0.053).

Both lovastatin and gemfibrozil significantly lowered VLDL cholesterol levels (28 and 41%, respectively, p <0.01 in each group compared with baseline). There was no significant difference in VLDL cholesterol levels between the lovastatin and gemfibrozil groups. However, in both groups, triglyceride and VLDL cholesterol levels were highly variable at baseline and during the study. Only gemfibrozil reduced triglyceride levels significantly (36%, p <0.01). The decrease in triglyceride levels was significantly greater with gemfibrozil than with lovastatin (p <0.01). There were 35 patients in the lovastatin group and 34 in the gemfibrozil groups with triglyceride levels <400 mg/dl in whom VLDL levels were measured by ultracentrifugation at baseline and during treatment. The ratio of VLDL to triglyceride would be expected to be 0.2.[21] At baseline, it was 0.168 ± 0.03 (mean ± standard deviation) in the lovastatin group and decreased after 24 weeks of treatment to 0.126 ± 0.04, a decrease of 24.6 ± 22.0% (p <0.01). In the gemfibrozil group, the ratio at baseline was 0.167 ± 0.05 and decreased to 0.138 ± 0.04, a decrease of 11.7 ± 27.5% (p <0.05). The lovastatin group tended to have a larger decrease in the ratio of VLDL to triglycerides (p = 0.09), suggesting a larger reduction in cholesterol than triglyceride in VLDL.

In the lovastatin-treated group, 15 patients had diabetes controlled with diet and 35 were taking oral agents. In the gemfibrozil group, 15 had diabetes controlled with diet and 37 were taking oral agents. The lipid changes in these groups were generally similar to each other and to the group as a whole with the following exceptions: The decrease in total cholesterol from baseline did not reach significance in the small number of patients controlled with diet who were treated with gemfibrozil, and the decrease in VLDL cholesterol was of significance (p <0.05) with lovastatin and of borderline significance with gemfibrozil (p <0.08) in these patients (Tables III and IV). There was no significant difference between lovastatin and gemfibrozil in glucose control during therapy as assessed by evaluation of the change in fasting glucose values and hemoglobin A$_{1c}$ from baseline to the end of treatment (Tables V, VI and VII).

Patients were questioned for adverse experiences at each visit. Both drugs were well tolerated. There were no serious clinical or laboratory adverse experiences in patients receiving lovastatin. One patient who received gemfibrozil developed confirmed cholecystitis and another developed an increase in liver enzymes with jaundice (maximal bilirubin 6.1 mg/dl) at the end of therapy, which resolved within a few weeks and was possibly due to gallbladder disease. One patient taking gemfibrozil developed a perforating ulcer and 1 required a mastecto-

TABLE V Glucose Control

	Treatment	No. of Pts.	Baseline Mean	SD	Week 24 Mean	Week 24 SD	Change % Mean	Change % SD	p Value (from Baseline)
Fasting blood glucose (mg/dL)	Lovastatin	50	169.9	43.6	177.3	57.5	4.9	23.6	NS
	Gemfibrozil	52	153.2	41.3	167.5	64.6	11.5	38.9	= 0.05
HbA$_{1C}$(%)	Lovastatin*	49	6.7	1.3	7.1	1.5	7.2	17.5	<0.01
	Gemfibrozil†	49	6.3	1.3	6.4	1.5	4.3	20.3	NS

* HbA$_{1C}$ was not measured in 1 patient during treatment.

† Three patients with variant hemoglobins were excluded from analysis of HbA$_{1C}$.

Note: There was no significant difference between treatment groups in the change from baseline for fasting blood sugar and HbA$_{1C}$.

HbA$_{1C}$ = hemoglobin A$_{1C}$; other abbreviations as in Table II.

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TABLE VI Glucose Control in Diet-Controlled Diabetics

					Week 24		Change %		
	Treatment	No. of Pts.	Baseline Mean	SD	Mean	SD	Mean	SD	p Value (from Baseline)
Fasting blood glucose (mg/dL)	Lovastatin	15	142.9	31.1	152.7	54.6	5.6	24.2	NS
	Gemfibrozil	15	129.3	31.4	155.6	63.8	22.3	54.4	<0.05
HbA_{1C}(%)	Lovastatin	14*	6.1	1.3	6.5	1.3	9.8	21.2	<0.05
	Gemfibrozil	15	5.4	1.1	6.3	1.7	15.4	21.0	<0.05

* HbA_{1C} was not measured during treatment in 1 patient.
Note: There was no significant difference between treatment groups in the change from baseline for fasting blood glucose or HbA_{1C}.
Abbreviations as in Tables II and V.

my for breast cancer which, in all probability, had existed before treatment. There was no lens change associated with a change in visual acuity noted in lovastatin-treated patients. One patient who was treated with gemfibrozil had a unilateral decrease in visual acuity with worsening of a lens opacity. Elevations in creatine phosphokinase values to >1,000 IU/liter were seen in 3 patients: 2 taking gemfibrozil and 1 taking lovastatin. No patient had signs of myopathy, and all CPK levels returned to baseline within a few weeks during continued therapy. At allocation, 1 additional patient had a creatine phosphokinase value >1,000 IU/liter, which declined during gemfibrozil therapy.

DISCUSSION

The results of this multicenter study involving 102 subjects demonstrate that lovastatin is a well-tolerated and effective cholesterol-lowering agent with a good safety profile in patients with well-controlled NIDDM and primary hypercholesterolemia. At a daily dose of 20 to 40 mg, lovastatin reduced total and LDL cholesterol by 20 and 26%, respectively. Compared with gemfibrozil, lovastatin had a significantly greater cholesterol-lowering effect. This was especially evident when comparing the LDL-lowering effect of lovastatin and gemfibrozil among patients whose LDL cholesterol was >190 mg/dl. The degree of reduction in total and LDL cholesterol by lovastatin was similar to that reported in nondiabetic patients.[8-10] In addition to its LDL-lowering efficacy, lovastatin treatment may offer an additional theoretical advantage of accelerating the rate of removal of LDL from the circulation, thereby reducing LDL particle exposure to the modifying effects of the diabetic milieu, e.g., glycosylation.[3-7,23]

In contrast, gemfibrozil led to a greater reduction in plasma triglyceride levels (excluding 1 patient with severe weight gain and hypertriglyceridemia). However, both drugs caused a similar reduction in VLDL cholesterol values. Although detailed lipoprotein composition was not measured in this study, these data suggest that lovastatin was more effective in reducing the concentration of cholesterol-enriched lipoprotein subpopulations in the ultracentrifugation fraction with density less than 1.006 g/ml. This is consistent with the known mechanisms of action of these drugs on triglyceride-rich lipoprotein metabolism. Gemfibrozil stimulates the lipolytic cascade,[24,25] whereas lovastatin enhances the removal of atherogenic cholesterol-rich VLDL remnants, the concentration of which is known to be increased in these patients,[15] through the B, E-receptor.[26]

Lovastatin and gemfibrozil both led to an increase in HDL cholesterol concentrations similar to that reported in nondiabetic subjects.[12-14,17] The mode of action by which gemfibrozil raises HDL levels is also thought to be related to the activation of lipolysis leading to transfer of surface material from triglyceride-rich lipoproteins into the HDL fraction.[24] Because lovastatin does not appear to stimulate this pathway, its effect on HDL probably involves a different mechanism. Both drugs produced reductions in the total/HDL cholesterol ratio, although the reduction tended to be greater with lovastatin due to its greater effect on cholesterol. This ratio correlates well with a reduction in the cardiovascular morbidity and mortality in intervention trials.[27-32]

Both agents were well tolerated. One patient who was treated with gemfibrozil developed definite symptomatic gallbladder disease and another developed possible cholecystitis. This effect has been previously reported with gemfibrozil in nondiabetic patients.[32] Given the increased frequency of silent cholelithiasis in diabetes,[33] it is possible that these patients had clinically undetectable gallstones before study entry since ultrasound evaluation was

TABLE VII Glucose Control in Patients Taking Oral Hypoglycemic Agents

					Week 24		Change %		
	Treatment	No. of Pts.	Baseline Mean	SD	Mean	SD	Mean	SD	p Value (from Baseline)
Fasting blood glucose (mg/dL)	Lovastatin	35	181.5	43.3	187.8	56.6	4.5	23.6	NS
	Gemfibrozil	37	162.9	41.2	172.4	65.2	7.1	30.4	NS
HbA_{1C}(%)	Lovastatin	35	6.9	1.2	7.3	1.5	6.2	16.1	<0.05
	Gemfibrozil	34*	6.6	1.3	6.5	1.4	−0.6	18.2	NS

* Three patients with variant hemoglobins were excluded from analysis of HbA_{1C}.
Note: There was no significant difference between treatment groups in the change from baseline for fasting blood sugar or HbA_{1C}.
Abbreviations as in Tables II and V.

not required for admission. None of the 3 patients with creatine phosphokinase elevations in this study had symptoms, and all cases resolved during continued therapy.

Although several drugs are available for the treatment of hypercholesterolemia in patients with diabetes, adverse effects limit their application and safety. Among these is the reported aggravation of glucose intolerance by niacin and fish oil. In this respect, lovastatin was shown to be without any deleterious effect.

Subjects with diabetes have an increased incidence of lens cataracts, and 1 study of lovastatin in dogs had suggested that the drug may predispose to the formation of posterior capsular opacities at very high doses (over 60 times the maximal human therapeutic dose). No lens opacification was noted with lovastatin treatment during the duration of the study.

The results of this study show lovastatin to be a well-tolerated drug in patients with NIDDM for the treatment of primary hypercholesterolemia. It was more effective than gemfibrozil in reducing LDL cholesterol and the ratio of total to HDL cholesterol. Both drugs had favorable effects on HDL and total cholesterol levels.

In addition to producing substantial reductions in LDL cholesterol, lovastatin apparently reduces the amount of cholesterol compared with triglyceride in lipoproteins, which might possibly reduce the levels of potentially atherogenic remnant lipoproteins.[19] Further work is needed to substantiate this possibility.

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A Multicenter Comparison of Lovastatin and Probucol for Treatment of Severe Primary Hypercholesterolemia

The Lovastatin Study Group IV

A multicenter study was undertaken to compare the effects of lovastatin (given in 4 different dosage regimens) and probucol in patients with severe primary hypercholesterolemia. The subjects were 290 patients taking lipid-lowering diets who were randomly assigned to 1 of the following treatment regimens for 14 weeks: lovastatin, 40 mg once a day with the morning meal (qam); lovastatin, 40 mg once a day with the evening meal (qpm); lovastatin 80 mg qpm; lovastatin, 40 mg twice daily, or probucol, 500 mg twice daily. One-third of the patients received probucol, and the other two-thirds were equally divided between the 4 lovastatin treatment groups. The mean reductions in total cholesterol in the 5 groups were, respectively, 20, 25, 30, 33 and 10%. The corresponding values for low-density lipoprotein cholesterol were 25, 32, 37, 40 and 8%. High-density lipoprotein cholesterol increased by 9 to 12% in all the lovastatin groups, but decreased by 23% in the probucol group. Triglycerides were reduced by 17 to 25% in all the lovastatin groups, but did not change significantly in the probucol group. Both drugs were well tolerated; no serious adverse events could be attributed to either agent. It is concluded that lovastatin is a considerably more effective lipid-lowering agent than probucol. In addition, lovastatin is almost as effective when given in a single daily dose as when given in a divided dose. When a once-a-day regimen is used, lovastatin is more effective if taken in the evening rather than the morning.

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Hypercholesterolemia (or, more accurately, an elevated low-density lipoprotein [LDL] cholesterol level) is a well-known, major risk factor for the development of ischemic heart disease. Moderate hypercholesterolemia can often be controlled by dietary therapy, but typical lipid-lowering diets reduce serum cholesterol by only approximately 15%.[1] Dietary therapy, therefore, is usually insufficient as the sole intervention for patients with substantially elevated serum cholesterol levels.

Lovastatin (previously known as mevinolin), a potent inhibitor of hydroxy-methylglutaryl-coenzyme A reductase, is available for prescription in Canada, the United States and several other countries. The effectiveness of lovastatin as a lipid-lowering agent in familial and nonfamilial hypercholesterolemia has been well documented in multicenter trials[2,3]; recently, another multicenter study showed that this drug is more effective and better tolerated than cholestyramine.[4] A fourth multicenter study[5] showed that lovastatin reduced total and LDL cholesterol more effectively than gemfibrozil; gemfibrozil, on the other hand, produced greater reductions in triglyceride levels and increases in high-density lipoprotein (HDL) cholesterol levels than lovastatin.

The multicenter study reported here compared lovastatin with probucol in a double-blind, controlled fashion. The efficiency of different lovastatin dosage regimens was also investigated. Previous studies[2,3] had suggested that lovastatin is slightly more effective when given in divided doses, compared with a single daily dose and that a single daily dose is more effective if given in the evening rather than the morning.[6] Results from 1 of the 13 centers participating in this trial (Helsinki University Central Hospital) were published previously,[7] and preliminary data from the Canadian centers have been published in summary form.[8] This paper gives a complete account of the study.

METHODS

Subjects: Each of 13 clinical centers contributed 8 to 60 patients, for a total of 290 patients. The subjects' age range was 23 to 69 years (mean 50), and 68% were men. All patients had primary hypercholesterolemia, with elevated LDL cholesterol levels and normal triglyceride concentrations (type IIa phenotype) or with mild hypertriglyceridemia (type IIb phenotype).[9] The patients were at high risk for myocardial infarction by virtue of meeting 1 of the following criteria: (1) LDL cholesterol level >4.27

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mmol/liter while receiving a standard lipid-lowering diet and evidence of significant coronary atherosclerosis (a positive exercise stress test result, angina pectoris, a history of myocardial infarction, coronary bypass surgery, angioplasty or coronary stenosis demonstrated on angiography, or both); (2) LDL cholesterol level >4.91 mmol/liter while on a diet and (a) currently smoking >10 cigarettes per day, (b) history of ischemic heart disease before age 60 years in 1 or more parents or siblings, or (c) peripheral vessel atherosclerosis demonstrated by bruits, ultrasound or angiography; or (3) LDL cholesterol level >5.56 mmol/liter while on a diet.

The principal exclusion criteria were as follows: premenopausal status in women, unless highly unlikely to conceive; a triglyceride level >3.95 mmol/liter, alcohol intake of >10 drinks per week, impaired hepatic function or abnormal results of liver function tests; myocardial infarction or coronary bypass surgery within the previous 4 months; or diabetes mellitus or glucose intolerance, defined as a fasting glucose level >7.8 mmol/liter.

Procedures: At least 6 weeks before the start of the study, the patients were withdrawn from all lipid-lowering drugs and given either the American Heart Association phase I diet or a more rigorous diet. They continued with dietary therapy (with regular visits to a dietitian for reinforcement of nutritional advice) throughout the study. All subjects received placebo that matched lovastatin capsules and placebo that matched probucol tablets for 4 weeks (weeks −4 to 0) in a single-blind fashion. The patients were then randomized to 1 of 5 treatments after having been stratified by diagnosis; those believed to have familial hypercholesterolemia formed stratum I and all others (including those believed to have familial combined hyperlipidemia) formed stratum II. Because of the difficulty of diagnosing familial hyperlipidemias in some cases, the best judgment of the clinician applied. The purpose of the stratification was to reduce the chance of obtaining significant differences in the baseline lipoprotein values of the 5 groups. The randomization schedule was organized in blocks of 5, so as to ensure that within each center the number of patients in each group was approximately equal. Lovastatin capsules and its placebo were formulated by Merck Sharp & Dohme Research Laboratories (Rahway, New Jersey). Probucol and its placebo were supplied in capsules by Merrell Dow Pharmaceuticals Inc. (Cincinnati, Ohio).

Patients were treated for 14 weeks with 1 of 5 therapeutic regimens: probucol, 500 mg twice daily; lovastatin, 40 mg once a day with the morning meal (qam); lovastatin, 40 mg once a day with the evening meal (qpm); and lovastatin, 80 mg qpm or lovastatin, 40 mg twice daily. Lovastatin was supplied as dry-filled capsules and probucol as tablets. The double-dummy technique was used to render the study double blind: patients randomized to lovastatin capsules also took a placebo tablet matching probucol twice daily, and those randomized to probucol tablets also took a capsule matching lovastatin twice daily. In the case of the once-each-morning regimen and the once-each-evening regimen, a placebo capsule matching lovastatin was taken in the evening and morning, respectively, to ensure that all patients took 1 capsule and 1 tablet twice daily. Test drug and placebo were taken immediately before the morning and evening meals. Adherence to therapy was monitored by capsule and tablet counts.

Lipid and apolipoprotein analysis: Patients visited the clinic in the morning of a fixed day during weeks −4, −2, 0, 2, 6, 10 and 14 after having fasted for at least 12 hours. The morning dose was postponed on those days until after a blood sample was drawn. Levels of total plasma cholesterol, HDL cholesterol and plasma triglycerides were measured in all samples. In addition, at weeks −2, 0, 10 and 14, ultracentrifugation was performed to permit determination of levels of LDL cholesterol and very low density lipoprotein (VLDL) cholesterol and samples were analyzed for levels of apolipoprotein (apo) AI, AII and B.

All lipid analyses for the United States studies were performed in a central laboratory (Evan A. Stein, MD, PhD, University of Cincinnati Medical Center). Lipid analyses for the Finnish and Canadian centers were performed in local laboratories. All apo assays (including those from centers in Finland and Canada) were performed in the United States Laboratory. The laboratory maintained the results of the lipid and apo analyses from week 2 onward and did not reveal them to the clinics or the coordinating center until the completion of the study.

Analytic techniques: All blood samples for lipid, lipoprotein and apo analyses were collected in sodium/potassium ethylenediaminetetraacetate (1 mg/ml). Samples were separated within 4 hours, and the plasma was transferred to polyethylene containers and stored at 4°C. For samples that required ultracentrifugation, plasma was added to vials containing predispensed azide and aprotinin (0.1 mg of azide and 3 μL of aprotinin per milliliter of plasma). Samples from United States centers were shipped to the central laboratory by overnight courier in polystyrene boxes with the temperature controlled at 4°C. On arrival at the laboratory, samples were immediately unpacked, stored at 4°C and usually analyzed the same day. In Canada and Finland, samples were analyzed at the local laboratories. Levels of plasma total cholesterol, HDL cholesterol and triglycerides were measured on an automated analyzer (Hitachi 705 in the United States[10] and Abbott ABA-100 in Canada)[11,12] by enzymatic procedures. In Finland, cholesterol levels were determined with the use of an enzymatic colorimetric method (CHOD-PAP method, Boehringer-Mannheim Diagnostics). HDL was isolated with the use of the heparin-2 molar manganese chloride procedure[13,14] to precipitate VLDL and LDL cholesterol. Preparative ultracentrifugation at a density of 1,006 kg/liter was performed at weeks −2, 0, 10 and 14. The VLDL cholesterol concentration was obtained from the difference between total cholesterol and the density fraction >1,006 kg/liter (LDL plus HDL). Both total cholesterol and density fractions >1,006 kg/liter were analyzed in the same run.

Levels of apo AI, AII and B were measured at weeks −2, 0, 10 and 14. Apo AI was quantitated with the use of

TABLE I Baseline Characteristics of Study Population

	Treatment Group					
Characteristic	Lovastatin 40 mg qam (n = 49)	Lovastatin 40 mg qpm (n = 47)	Lovastatin 80 mg qpm (n = 49)	Lovastatin 40 mg bid (n = 48)	Probucol 500 mg bid (n = 97)	All Patients (n = 290)
Mean age (yr)	48.0	52.5	49.1	51.0	49.4	49.8
Sex (male/female)	34/15	29/18	33/16	34/14	68/29	198/92
Mean weight (kg)	73.5	74.5	74.1	77.7	76.3	75.4
No. with familial hypercholesterolemia*	33	32	31	32	61	189
No. with familial combined hyperlipidemia*	2	2	2	2	5	13
No. with polygenic hypercholesterolemia	14	13	16	14	31	88

* Based on best judgment of investigators, not strict diagnostic criteria.
qam = morning meal; qpm = evening meal.

electroimmunoassay,[15] and apo AII and B with the use of enzyme-linked immunosorbent assay.[16,17]

Clinical and laboratory monitoring: At every visit, each patient was asked about adverse experiences, which were rated as either definitely, probably, possibly, probably not or definitely not drug-related. A complete blood cell count and urinalysis were performed at every visit at each center. Levels of bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase and creatinine were determined at each visit. In addition, at weeks −2, 0, 2, 6 and 14, platelet count, prothrombin time and partial thromboplastin time were determined locally, and levels of serum total protein, uric acid, fasting glucose, thyroxine, sodium, potassium, chloride, bicarbonate, calcium and phosphate levels were determined. Serum chemistry analyses were performed at the central laboratory for the United States centers and locally for the Canadian and Finnish centers.

Pulse rate, blood pressure and weight were recorded at each visit. Electrocardiograms were recorded at weeks 0, 2 and 14. A full ophthalmologic examination, including slit-lamp examination of the lens and measurement of corrected visual acuity, was performed before and after active treatment. The ophthalmologists did not have access to the treatment allocation schedule.

Statistical analysis: The data were analyzed by the coordinating center (Merck Sharp & Dohme Research Laboratories). Changes from baseline were calculated from the last value of the placebo baseline period (week 0) using the intention-to-treat approach. In the few cases in which a patient did not complete the study or in which data were missing, the last value was carried forward. All pairwise comparisons among treatment groups for continuous variables were performed using an analysis of variance on the ranks (ranking without regard to clinic or treatment), with treatment and clinic as model effects. The Fisher exact test was used for the analysis of binary data (e.g., adverse experience counts). For the analysis of new lens opacities, a maximal likelihood procedure, which allows for misclassification error, was used based on the method of Yanagawa et al.[18] Changes from baseline within treatment groups were analyzed using a multiclinic extension of the Wilcoxon signed-rank test.[19] There was no adjustment for multiple comparisons, because each comparison was specified in advance. All tests were 2-sided.

Where percent changes were approximately normally distributed, central tendency is expressed as the arithmetic mean percent change and 95% confidence intervals are given; where skewed distributions of treatment percent changes were observed, the median is used. Where medi-

TABLE II Baseline Lipoprotein Values of the Study Population

	Treatment Group					All Patients		
	Lovastatin				Probucol			
Lipoprotein	40 mg qam	40 mg qpm	80 mg qpm	40 mg bid	500 mg bid	Week 0	Week −2	Week −4
Total-C*	9.45	9.57	9.76	9.38	9.54	9.50	9.54	9.55
LDL-C*	7.49	7.67	7.76	7.46	7.55	7.54	7.53	7.47
HDL-C*	1.12	1.26	1.15	1.08	1.14	1.15	1.15	1.15
LDL-C/HDL-C*	7.2	6.4	7.1	7.4	7.1	7.05	7.01	6.99
VLDL-C†	0.65	0.52	0.80	0.72	0.79	0.71	0.70	—
Triglycerides†	1.62	1.33	1.51	1.57	1.75	1.55	1.60	1.56
Apo AI†	127	133	137	135	130	133	136	—
Apo AII†	45	41	52	45	45	45	47	—
Apo B†	176	186	209	200	192	195	194	—

* Mean; † Median.
Units are mmol/liter except those for apolipoproteins, which are mg/dl. Week 0 values were used to calculate means or medians for the treatment groups.
Apo = apolipoprotein; C = cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; qam = morning meal; qpm = evening meal; VLDL = very low density lipoprotein.

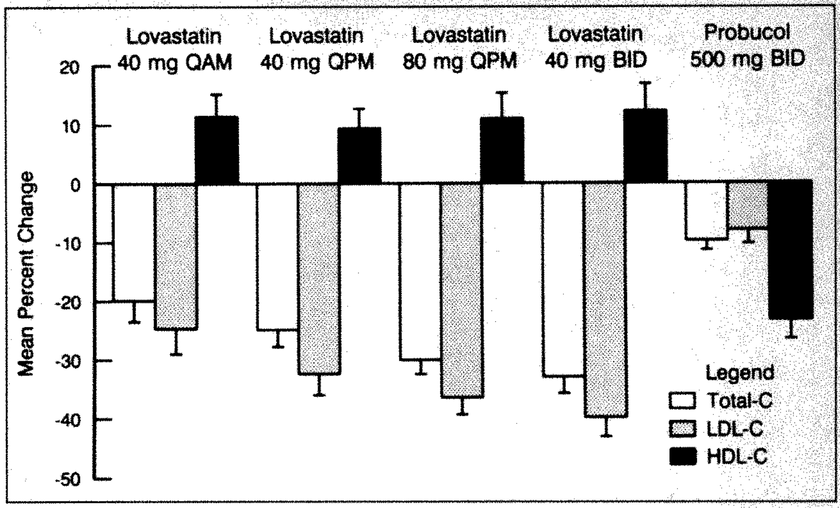

FIGURE 1. Mean percent changes with 95% confidence intervals in levels of total cholesterol (C) (*open bars*), low-density lipoprotein cholesterol (LDL-C) (*stippled bars*) and high-density lipoprotein cholesterol (HDL-C) (*solid bars*). QAM = morning meal; QPM = evening meal.

an percent changes are displayed, baseline values also are given as medians. The confidence intervals for the medians are not displayed because there is no standard method for deriving the confidence interval for the median of a skewed distribution.

RESULTS

The characteristics and baseline lipoprotein values of the patients in the 5 treatment groups and in the study population as a whole are summarized in Tables I and II. The groups were generally similar with regard to baseline characteristics, except for the average age of patients in the lovastatin 40 mg qam group, which differed significantly ($p \leq 0.05$) from that of patients in the lovastatin 40 mg qpm group. Lipid variables were generally similar at baseline among the groups, except for HDL cholesterol in the groups receiving lovastatin 40 mg qam vs lovastatin 40 mg qpm ($p \leq 0.01$). The lipoprotein values were similar at weeks −4, −2 and 0, indicating a stable baseline. Of the patients studied, 97% had severe hypercholesterolemia, defined as a baseline plasma cholesterol level >6.72 mmol/liter.[20] In addition, 98% of the patients were white and 72% had a history of ischemic heart disease. The study was completed by 283 of the 290 subjects enrolled. Three patients in the probucol treatment group and 1 in the lovastatin 40 mg twice daily group did not complete the study because of adverse events; in addition, 1 was withdrawn because of noncooperation, 1 because of surgery (endarterectomy) and 1 because of a protocol violation (LDL cholesterol decreased 26% while the patient was still in the placebo run-in period). Analyzable lipid data, using the all-patients-treated approach, were available for 289 patients. The average dose actually taken (based on medication returned) was estimated to be 96, 96, 93, 95 and 95% of the specified dose for the lovastatin 40 mg qam, lovastatin 40 mg qpm, lovastatin 80 mg qpm, lovastatin 40 mg twice-daily and probucol 500 mg twice-daily groups, respectively. Compliance was thus good and similar in all groups.

Effects on lipoproteins: The effects on lipoproteins after 14 weeks of treatment are shown in Figures 1 and 2. The primary variables of interest were total and LDL

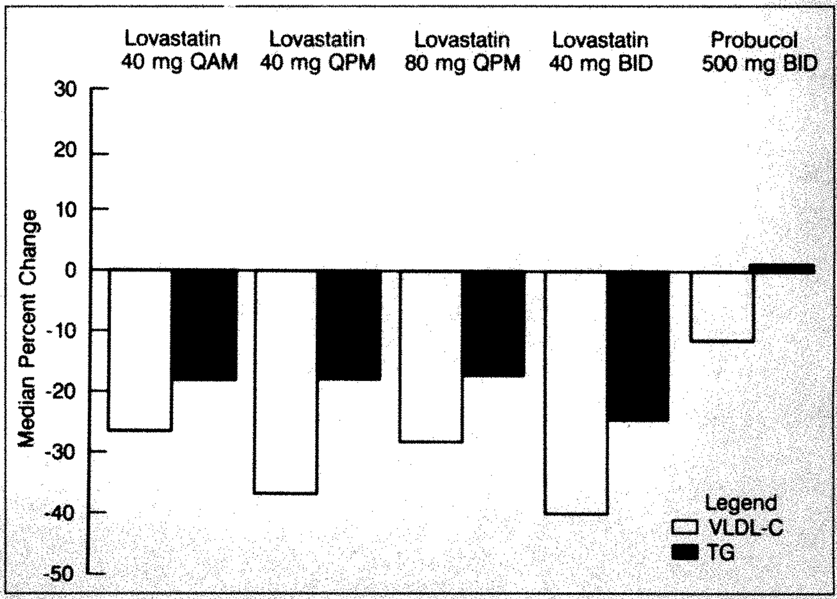

FIGURE 2. Median percent change in very low density lipoprotein cholesterol (VLDL) (*open bars*) and plasma triglycerides (TG) (*solid bars*). Other abbreviations as in Figure 1.

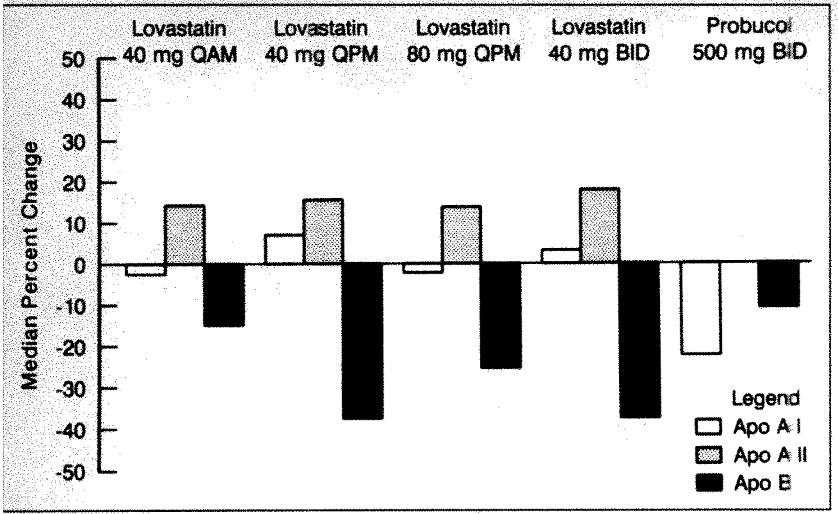

FIGURE 3. Median percent changes in apolipoprotein AI (Apo AI) (*open bars*), apolipoprotein AII (Apo II) (*stippled bars*) and apolipoprotein B (Apo B) (*solid bars*). Other abbreviations as in Figure 1.

cholesterol levels, which were reduced (p ≤0.01) in all 5 treatment groups (Fig. 1). The differences in percent change in mean total and LDL cholesterol were highly significant between each of the lovastatin treatment groups vs probucol (p ≤0.01). The effects of lovastatin therapy were considerably greater than those of probucol: at week 14, total cholesterol decreased 20 to 33% in the lovastatin groups vs 10% in the probucol group. Reduction of LDL cholesterol was 3 to 5 times greater with lovastatin than with probucol. When the lovastatin regimens were compared, at week 14, 80 mg qpm was only slightly less effective than was 40 mg twice daily (LDL cholesterol was reduced 37 vs 40%), respectively, and the difference was not statistically significant (p >0.10). The lovastatin 40 mg qpm regimen tended to be more effective in reducing LDL and total cholesterol than was the 40 mg qam regimen (borderline significance, p = 0.06). Lovastatin 80 mg qpm reduced mean total cholesterol more than 40 mg qpm (p <0.05) did, but for LDL cholesterol the difference was not quite significant (p = 0.08).

By week 14, HDL had decreased 23% in the probucol group but had increased (9 to 12%) in all lovastatin groups. All changes from baseline were significant (p ≤0.05), with the exception of the change observed with lovastatin 40 mg qam at week 2, which was of borderline significance (p = 0.06). The percent change from baseline in HDL cholesterol was also significantly greater for each of the lovastatin treatment groups compared with the probucol group (p ≤0.01). None of the differences between the lovastatin treatments was significant. The mean LDL/HDL cholesterol ratio at week 14 was reduced 32, 38, 41 and 45% with lovastatin 40 mg qam, 40 mg qpm, 80 mg qpm and 40 mg twice daily, respectively, whereas this ratio increased 26% in the probucol group.

Changes in VLDL cholesterol and plasma triglyceride levels are presented in Figure 2. Decreases in VLDL levels from baseline occurred in all 5 treatment groups, but were significant (p ≤0.01) only in the lovastatin 80 mg qpm and 40 mg twice-daily groups. The percent decreases in VLDL levels from baseline were significantly greater (p <0.05) in all lovastatin groups than in the

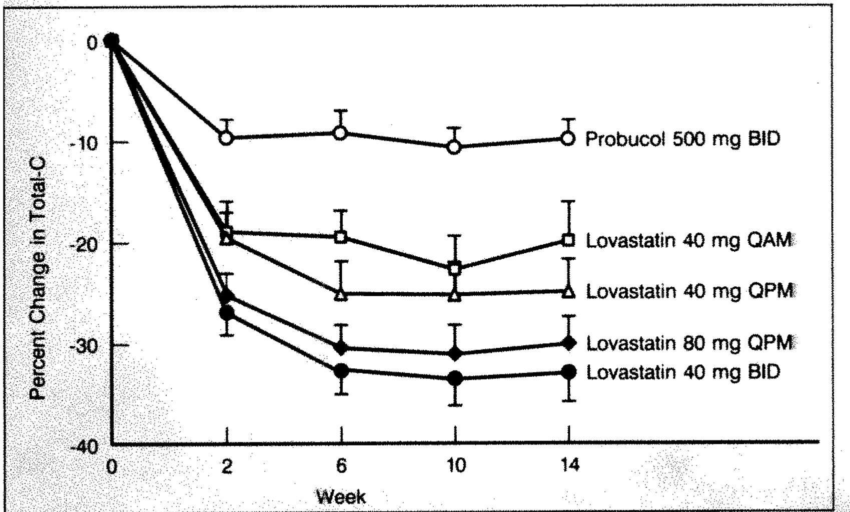

FIGURE 4. Mean percent change in total plasma cholesterol over time, with 95% confidence intervals. Abbreviations as in Figure 1.

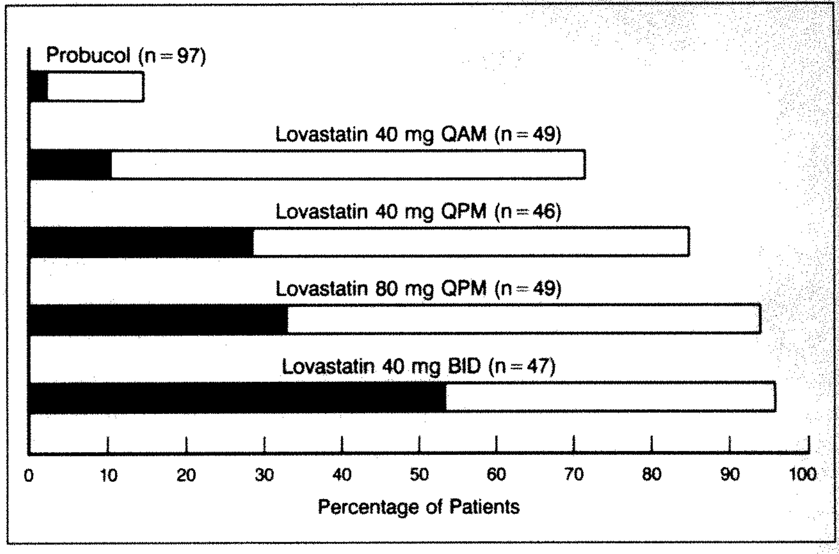

FIGURE 5. Percentages of patients achieving different degrees of response to the 5 treatment regimens. *Shaded plus open bars* indicate patients achieving at least a 20% reduction in low-density lipoprotein cholesterol levels at week 14. *Shaded bar alone* indicates those achieving at least a 40% reduction. Abbreviations as in Figure 1.

probucol group. Significant ($p < 0.05$) decreases in triglyceride levels from baseline occurred in each of the lovastatin groups, but not in the probucol group. The percent decreases in triglyceride levels were significantly greater ($p < 0.01$) in all lovastatin groups than in the probucol group. (Because the distributions of changes in the levels of VLDL cholesterol, plasma triglyceride and apo were substantially skewed, medians of the changes in these variables were considered a better measure of central tendency and are shown in Figures 2 and 3.) Effects on apo AI, AII and B are shown in Figure 3. Levels of apo B decreased significantly in all treatment groups ($p < 0.01$), but more so in all lovastatin groups than in the probucol group ($p < 0.01$). Apo AI did not change significantly in any of the lovastatin groups, but decreased by 22.4% ($p < 0.01$) in the probucol group. Apo AII increased in all lovastatin groups ($p < 0.05$), but did not change significantly in the probucol group. With respect to apo AII, each lovastatin group was significantly different from the probucol group ($p < 0.05$).

Figure 4 shows the time course of the effects on total cholesterol levels. The maximal reduction in total cholesterol levels was achieved by week 6.

Figure 5 shows the percentage of patients in the 5 treatment groups who experienced reductions of ≥20 or ≥40% in LDL levels at week 14. A ≥20% reduction in LDL cholesterol was achieved by only 14% of patients in the probucol group vs the majority (71 to 96%, depending on dose) of those in each of the 4 lovastatin groups. Reductions of ≥40% were observed in more than half the patients taking lovastatin, 40 mg twice daily, compared with only 2% of the patients taking probucol. Reductions of ≥60% in LDL cholesterol levels were observed in only 3 patients—2 who received lovastatin, 40 mg twice daily, and 1 who received lovastatin, 40 mg qpm.

Adverse events: Serious clinical adverse events were reported for 4 patients: 2 in the probucol group and 1 each in the lovastatin 40 mg qam and 40 qpm groups. In the lovastatin 40 mg qpm group, a 38-year-old woman who had previously undergone a hysterectomy was diagnosed as having an ovarian cyst on day 30 of treatment; the cyst was surgically removed. The second patient who experienced a serious adverse event while taking lovastatin was a 58-year-old man who underwent percutaneous transluminal angioplasty on day 7 of treatment. This patient had a history of sporadic exertional and stress-related midabdominal pain that occurred more frequently just before his entering the study. A 56-year-old man in the probucol group who experienced severe diarrhea, gastrointestinal cramps and nausea was admitted to the hospital and diagnosed as having gastroenteritis. The last patient with a serious clinical adverse event was a 52-year-old man who experienced left-arm pain on day 61 of probucol treatment. He was admitted to the hospital for 1 day, and the results of all electrocardiographic and laboratory tests were normal. His experience was attributed to fatigue. The investigators did not consider any of these adverse events to be drug-related and all 4 patients continued on their respective therapeutic regimens.

With few exceptions, drug-attributable nonserious adverse events (i.e., those considered definitely, probably or possibly drug-related) were confined to the gastrointestinal tract. Significantly ($p \leq 0.05$) more cases of drug-attributable diarrhea occurred with probucol ($n = 8$) than with any of the lovastatin regimens. Only 1 patient, in the lovastatin 80 mg qpm group, reported diarrhea that the investigator attributed to the drug. Significantly ($p \leq 0.05$) more drug-attributable cases of flatulence occurred with lovastatin 40 mg qam ($n = 5$) and 40 mg twice daily ($n = 5$) than with probucol ($n = 2$). Also, a significantly ($p \leq 0.05$) higher proportion of patients developed rash attributed to lovastatin, 40 mg twice daily ($n = 3$), than did those taking probucol (none). One case of drug-attributable rash occurred in each of the other lovastatin groups (40 mg qam, 40 mg qpm and 80 mg qpm). Myalgia was reported in only 1 lovastatin-treated patient, who had an upper respiratory tract infection and was not accompanied by creatine kinase values outside

TABLE III Mean Baseline (Week 0) Values and End-Of-Treatment Changes (Week 14) in Serum Enzyme Levels

	Enzyme			
Treatment Group	AST	ALT	AP	CK
Lovastatin (40 qam)				
Week 0	19.9	19.8	79.8	102.3
Week 14	+1.1*	+1.7*	+0.9	+10.0
Lovastatin (40 qpm)				
Week 0	20.1	21.1	82.1	101.1
Week 14	+2.5†	+3.2‡	−2.0	+3.1
Lovastatin (80 qpm)				
Week 0	18.5	20.0	80.2	89.8
Week 14	+2.9*	+2.3†	−3.6*	+26.9†
Lovastatin (40 bid)				
Week 0	19.7	19.7	87.1	103.4
Week 14	+3.7*	+5.9*	−0.7	+49.3†
Probucol (500 mg bid)				
Week 0	18.2	19.0	80.3	89.6
Week 14	+0.8	+0.6	−4.7*	+16.9

* p ≤ 0.01, different from zero; † p ≤ 0.05, different from zero; ‡ p = 0.09, different from zero.

Values are in U/liter.

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CK = creatine kinase; qam = morning meal; qpm = evening meal.

TABLE IV Results of Examination of the Lens

		No. (%) of Patients with Lens Opacities			
Treatment Group	No. of Pts.	Baseline	New	Lost	Poststudy
Lovastatin (40 qam)	45	6 (13.3)	3	1	8 (17.8)
Lovastatin (40 qpm)	42	14 (33.3)	1	2	14 (33.3)
Lovastatin (40 bid)	42	11 (26.2)	2	1	13 (31.0)
Lovastatin (80 qpm)	46	13 (28.3)	4	3	13 (28.3)
Probucol	87	24 (27.6)	4	6	22 (25.3)

Values in parentheses represent prevalence of lens opacities (unilateral or bilateral of any type or size). New opacities are those reported at the poststudy examination but not at baseline and lost opacities are those reported at baseline but not at the poststudy examination. Because some patients were reported to have unilateral opacities at baseline and bilateral opacities poststudy or vice versa, the poststudy value does not necessarily equal baseline plus new opacities minus lost opacities.

Abbreviations as in Table I.

the normal range. Sleep disturbance (insomnia) was reported in 1 patient taking probucol and was attributed to the drug.

Four patients (3 taking probucol and 1 taking lovastatin, 40 mg twice daily) were withdrawn from the study due to clinical adverse events. The patient treated with lovastatin developed a rash 2 days after starting treatment. The clinic staff believed that the rash was probably drug-related and discontinued therapy. One patient in the probucol group was withdrawn because of headaches and 1 because of gastrointestinal pain. The third probucol-treated patient discontinued therapy because of headaches, insomnia and fecal incontinence.

The effects of the treatments on serum enzyme levels are shown in Table III. Mean increases in AST and ALT from baseline were significantly ($p \leq 0.01$) larger with all lovastatin regimens than with probucol. ALT tended to increase more than AST. Two patients taking lovastatin (both taking 40 mg qpm) and 2 taking probucol had increases in AST that were more than 50% above the upper limit of normal on 1 or more occasions. Eight patients taking lovastatin and 4 taking probucol had increases in ALT >50% above the upper limit of normal on 1 or more occasions. Only 1 patient had an increase in transaminases to more than 3 times the upper limit of normal: ALT was 3.6 times the upper limit of normal on a single occasion after 7 weeks of lovastatin, 80 mg qpm, and returned to normal without an interruption in therapy. Therapy with both probucol and lovastatin, 80 mg qpm, was associated with a significant decrease ($p \leq 0.01$) in alkaline phosphatase from baseline. Both the lovastatin 80 mg qpm and 40 mg twice-daily groups experienced significant ($p < 0.05$) increases in creatine kinase. In the 40 mg twice-daily group, the increase in serum creatine kinase was of boderline significance ($p = 0.09$) when compared with that in the probucol group.

Mean changes in blood pressure, pulse and weight from baseline to the end of the 14-week study were also analyzed. Mean body weight increased significantly ($p \leq 0.05$) in all treatment groups, except for the lovastatin 80 mg qpm group, in which the increase approached significance ($p = 0.08$). Mean increases in body weight ranged from 0.4 to 0.8 kg among the treatment groups. The between-group differences were not significant. In all treatment groups, changes from baseline in pulse and systolic and diastolic blood pressure were not significant.

Table IV shows the prevalence of lens opacities before and after treatment, as well as the number of patients with "new" lens opacities (opacities reported at the poststudy examination but not at baseline). New opacities were observed with both drugs, but no significant differences were observed among groups.

DISCUSSION

Both study drugs reduced total plasma and LDL cholesterol, but the effects of lovastatin were much greater at all dosage levels than were those of probucol. The between-drug difference was particularly pronounced with lovastatin, 80 mg/day; lovastatin, 40 mg twice daily, produced a fivefold greater reduction in LDL cholesterol when compared with probucol (40 vs 8%, respectivey). In addition, all 4 lovastatin treatment groups had significant increases in HDL cholesterol, whereas HDL cholesterol decreased substantially in the probucol-treated group. Levels of VLDL cholesterol and triglycerides were reduced (in most cases significantly) in all lovastatin-treated groups, but no significant changes occurred in the probucol-treated group. Apo B levels were reduced to a greater extent in the lovastatin-treated groups than in the probucol-treated group, and the reduction in all the lovastatin groups was significant. Apo AII levels, but not apo AI levels, increased appreciably in the lovastatin-treated groups, consistent with the effect on HDL cholesterol. Probucol produced a marked decrease in apo AI and had no significant effect on apo AII. The effects of both drugs on lipoproteins were consistent with the results of previous controlled studies of each agent separately[2-5,21,22] and the results of a small comparative study.[23] The effects of lovastatin were dose-related for total cholesterol and LDL cholesterol, but no clear dose-response relation was seen with regard to HDL cholesterol, VLDL cholesterol, triglycerides or apo AII and B. This lack of a dose-response relation may be due to the fact that, for all these variables, the response to lovastatin was smaller, or more variable, or both, when compared with the effects of the drug on total and LDL cholesterol. Alternatively, lovastatin may already be exerting maximal effects at 40 mg/day, so that no further effect would occur with 80 mg/day. Weak or absent dose-response relationships for these variables (except apo B) have also been observed in previous large studies of lovastatin.[2-4]

When the effects on the primary variable (LDL cholesterol) are compared, it is evident that lovastatin, 80 mg once a day, produced a reduction only marginally (and not significantly) less than that seen with 40 mg twice daily (37 vs 40%, respectively). Previous studies have demonstrated that 40 mg once a day is slightly (but significantly) less effective than 20 mg twice a day.[2,3] It is possible that the differential efficiency of once- vs twice-daily dosage regimens narrows as the dose-response curve ascends. When the 40 mg qam and qpm dosage regimens are compared, it appears that evening dosing is more efficient than morning dosing, although the difference did not quite reach statistical significance ($p = 0.06$). However, given that Illingworth[6] observed a similar effect, which also did not quite achieve statistical significance, the difference is probably real. A possible explanation may be found in the fact that cholesterol biosynthesis in humans reaches a peak around midnight.[24]

Both lovastatin and probucol were well tolerated in this study and no serious drug-related adverse events occurred. Few differences in the incidence of clinical adverse events were apparent between the 2 drugs, but lovastatin slightly increased mean transaminase values at all dosage levels, whereas probucol did not. Similarly, lovastatin, 40 mg twice daily and 80 mg qpm, produced a small but significant increase in creatinine kinase, but probucol did not. These effects of lovastatin have also been observed in previous studies.[2-5]

Lovastatin has caused marked, but asymptomatic, increases in hepatic transaminases in 1.9% of patients in clinical trials and a myopathy in 0.5% of patients (most of whom were also taking immunosuppressive agents, including cyclosporine, gemfibrozil or niacin).[25] In the present study, increases above 3 times the upper limit of normal in transaminase levels were observed in only 1 patient receiving lovastatin, and myopathy did not occur. A single patient taking lovastatin reported myalgia, but this occurred in association with a respiratory tract infection and was not accompanied by an increase in creatine kinase.

The increases in transaminases and creatine kinase were asymptomatic and did not cause any patient to withdraw from the study. Thus, these changes were of little clinical significance. Transaminase increases of sufficient magnitude to require withdrawal of lovastatin therapy have usually occurred after a longer treatment period than the 14-week duration of this study.[25]

Schaefer[26] recently reported a shortening of the sleep period, without difficulty in falling asleep, in 9 of 51 patients taking lovastatin. No randomized control group was used. In our double-blind, randomized, controlled study, only 1 case of sleep disturbance was reported and this occurred in a patient taking probucol.

The lens examinations did not reveal consistent changes. "New" and "lost" opacities were noted in all treatment groups. Probucol has been in widespread clinical use for many years and has not been reported to cause lens opacities. Prolonged follow-up[25] of the patients in our study as well as those in other studies[2-5] has likewise not established a causal relation between lovastatin and opacities of the human lens. As discussed elsewhere,[4,25] the new and lost opacities reported in our study are probably the result of small, clinically insignificant opacities being missed at either the baseline examination or the post-treatment examination. Thus, no evidence of any effect of lovastatin on the lens was apparent in this trial.

Lovastatin was clearly a much more effective lipid-lowering agent than was probucol, confirming (by means of a direct double-blind comparison) the results of previous studies. In addition, HDL cholesterol increased with lovastatin, but decreased with probucol. Because HDL cholesterol is inversely associated with coronary risk,[27] an increase in HDL has generally been regarded as desirable and a decrease as undesirable. This view may be too simple, however, because the effects of changes in HDL on the development of atherosclerosis may well depend on the mechanism that causes the change. For example, in theory, HDL cholesterol could decrease because of great uptake of HDL by the liver; conversely, HDL cholesterol could increase if hepatic uptake was impaired. Because the beneficial effect of HDL is postulated to result from its role in reverse cholesterol transport, greater hepatic uptake would be expected to be beneficial, even though the HDL cholesterol level decreased. The mechanisms by which both probucol and lovastatin alter HDL cholesterol levels remain unclear.

In summary, this study demonstrates that while both probucol and lovastatin are usually well tolerated, lovastatin is much more effective as a lipid-lowering agent. On the other hand, probucol may have additional beneficial effects on lipoproteins, perhaps by virtue of its antioxidant effect.[28] However, neither drug has been shown to reduce coronary heart disease in controlled clinical trials.

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Use of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in Various Forms of Dyslipidemia

Scott M. Grundy, MD, PhD, Gloria Lena Vega, PhD, and Abhimanyu Garg, MD

The inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase are highly effective in treating severe elevations of serum cholesterol, and are being widely used for this purpose. In our laboratory, these drugs have been used for the treatment of other forms of dyslipidemia including primary moderate hypercholesterolemia, primary mixed hyperlipidemia, diabetic dyslipidemia, hyperlipidemia of the nephrotic syndrome, and primary hypoalphalipoproteinemia. In these conditions, the HMG CoA reductase inhibitors proved effective in substantially decreasing levels of both low-density lipoproteins and very low density lipoproteins, as well as apolipoprotein B. In some patients, they may even increase levels of high-density lipoproteins. The primary mode of action of HMG CoA reductase inhibitors appears to be to increase the synthesis of hepatic receptors for lipoproteins containing apolipoprotein B, although a reduction in synthesis of these lipoproteins has not been ruled out with certainty. Regardless of mechanisms, drugs of this type appear to have the potential for effective therapy of various forms of dyslipidemia beyond primary severe hypercholesterolemia.

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The inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase are a new class of drugs that are highly effective for the treatment of hypercholesterolemia. The first drug of this class to be released in the United States was lovastatin. Recently, an analog, simvastatin, has been approved for use in several European countries. Because of their high efficacy, use of these drugs has increased rapidly, and already more than a million people are taking lovastatin in the United States alone. Although the HMG CoA reductase inhibitors have been recommended primarily for treatment of severe hypercholesterolemia, in clinical practice they undoubtedly are being used in patients with various other forms of dyslipidemia. Even so, their potential value for treatment of different forms of dyslipidemia, other than severe hypercholesterolemia, has not been investigated systematically in large numbers of well-defined patients. For this reason, we have performed a series of studies in patients with various types of dyslipidemia to explore the range of potential value of HMG CoA reductase inhibitors. None of our findings can be called definitive, but they do provide insights into possible utility of these drugs. In most of our studies, lovastatin was the drug investigated, but our findings almost certainly can be extended to other HMG CoA reductase inhibitors as well.

Investigations in our laboratory also have been directed toward learning the mechanisms whereby HMG CoA reductase inhibitors produce a reduction in plasma cholesterol levels. Studies in tissue culture and laboratory animals strongly suggest that the primary action of these agents is to increase the synthesis of low-density lipoprotein (LDL) receptors.[1] This response results from their action to inhibit cholesterol synthesis. Our isotope-kinetic investigations support this general mechanism. Our data, however, do not rule out the possibility that a lesser action of HMG CoA reductase inhibitors is to partially inhibit the synthesis of lipoproteins by the liver. Both mechanisms are consistent with the observation that reductase inhibitors lower serum concentrations of both LDL and very low density lipoproteins (VLDL). It must be recalled that VLDL particles, which contain apolipoprotein (apo) E as well as apo B, actually have a greater affinity for LDL receptors than LDL itself, which has only apo B. The action of HMG CoA reductase inhibitors to reduce VLDL levels, as well as LDL, may expand their potential use. Finally, there are reports that these agents will increase high-density lipoprotein (HDL) cholesterol concentrations in some patients. In the discussion to follow,

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TABLE I Plasma Lipid and Lipoprotein Levels in Eight Patients with Heterozygous Familial Hypercholesterolemia

	Control (mg/dl)	Lovastatin + Colestipol (mg/dl)
Total cholesterol	367 ± 31	208 ± 18*
Triglycerides	142 ± 19	140 ± 24
LDL cholesterol	321 ± 32	154 ± 19*
HDL cholesterol	27 ± 3	35 ± 5†

* $p <0.001$ vs control.
† $p <0.005$ vs control.
Values are expressed as mean ± standard error of the mean.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Adapted from *Ann Intern Med.*[10]

TABLE II Plasma Lipid and Lipoprotein Levels in 10 Patients with Heterozygous Familial Hypercholesterolemia

	Control (mg/dl)	Lovastatin + Colestipol (mg/dl)
Total cholesterol	357 ± 18	211 ± 14*
Triglycerides	152 ± 17	164 ± 24
VLDL cholesterol	57 ± 8	38 ± 5*
LDL cholesterol	265 ± 17	139 ± 14*
HDL cholesterol	36 ± 5	36 ± 4

* $p <0.05$ vs control.
Values are expressed as mean ± standard error of the mean.
VLDL = very low density lipoprotein; other abbreviations as in Table I.
Adapted from *Arteriosclerosis.*[11] *with permission from the American Heart Association.*

the potential indications for HMG CoA reductase inhibitors thus can be considered.

HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

This disorder is characterized by autosomal dominant inheritance of severe hypercholesterolemia.[2] A deficiency of LDL receptors underlies this condition.[3] Affected patients have inherited a defect in the gene encoding for LDL receptors from one parent. The allele derived from the other parent is normal. As a consequence of one defective gene, half the normal number of LDL receptors is synthesized and serum LDL cholesterol increases to twice normal levels. Patients with familial hypercholesterolemia (FH) frequently develop tendon xanthomas and premature atherosclerosis. Coronary artery disease (CAD) occurs frequently in men aged 30 to 40 years, and in women about 10 years older. Reduction of LDL cholesterol concentrations by drug therapy beginning in adolescence, therefore, is justified in patients with heterozygous FH.[2]

In the teenage years, bile acid sequestrants are first-line therapy for this disorder. The safety of HMG CoA reductase inhibitors in this age group remains to be determined. After age 20, however, reductase inhibitors can be justified for most male patients with heterozygous FH. The same is true for women after age 30 or 40. In moderate doses (20 mg twice daily), these drugs reduce LDL cholesterol levels about 30%.[4-6] A multicenter trial has documented the efficacy in cholesterol reduction and general safety of reductase inhibitors in patients with heterozygous FH.[7] Studies in our laboratory[6] indicate that these drugs promote LDL receptor-mediated clearance of LDL in FH heterozygotes as their primary mechanism for serum cholesterol reduction. Although reductase inhibitors are highly effective in patients with FH, LDL cholesterol concentrations remain moderately elevated in most despite therapy. Normalization of LDL cholesterol levels in many FH heterozygotes therefore requires more aggressive therapy than the use of reductase inhibitors alone.

Studies of the potential of drug therapy in FH heterozygotes have revealed that the combination of bile acid sequestrants and HMG CoA reductase inhibitors is unusually effective, and, with this regimen, LDL cholesterol concentrations usually fall within the normal range.[8-12] This is illustrated in 2 studies[10,11] performed in our laboratory (Tables I and II). In both studies, FH heterozygotes were treated with the combination of lovastatin plus a bile acid sequestrant. This drug combination was accompanied by few, if any, adverse effects; most patients tolerated it without difficulty. Both drugs seem to enhance the activity of LDL receptors and, consequently, the number of receptors expressed on liver cells doubles. As a result, as shown in these studies, LDL concentrations decrease approximately 50%. Thus, combined drug therapy probably represents the best available approach to treatment of severe hypercholesterolemia in FH heterozygotes.

PRIMARY SEVERE HYPERCHOLESTEROLEMIA

Severely elevated concentrations of LDL cholesterol often occur in patients who do not have classic heterozygous FH. Serum cholesterol levels in these persons are about 75% above the desirable level. Tendon xanthomas rarely are present, but premature CAD frequently occurs. The latter typically manifests itself in men aged 40 to 50 years, but later in women. Defects in the LDL receptor gene need to be documented in this condition, although it is possible that many patients have abnormalities in the primary structure of LDL receptors; if so, their defects are not as functionally severe as those found in classic heterozygous FH. Some patients with moderately severe hypercholesterolemia have abnormalities in the primary structure of the apo B molecule[13-15]; in this circumstance, LDL particles fail to bind normally to LDL receptors. A third possible cause of severe hypercholesterolemia is metabolic suppression of LDL receptor activity.[16] Thus, severe hypercholesterolemia appears to be due to many factors. The common occurrence of premature CAD in patients with primary severe hypercholesterolemia with marked elevations of LDL cholesterol justifies intervention with drug therapy.

Treatment of primary severe hypercholesterolemia of the non-FH type should be similar to that for heterozygous FH. Bile acid sequestrants are the drug of first choice.[17] If LDL cholesterol levels fail to decrease to the desirable range, which frequently occurs, HMG CoA reductase inhibitors should be added to the regimen. This combined drug therapy usually normalizes LDL levels in patients with severe hypercholesterolemia.[18] In patients

TABLE III Plasma Lipid and Lipoprotein Levels in 12 Patients with Primary Moderate Hyperlipidemia

	Placebo (mg/dl)	Lovastatin (mg/dl)
Total cholesterol	263 ± 7	204 ± 10*
Total triglycerides	136 ± 10	133 ± 10
LDL cholesterol	197 ± 7	134 ± 11*
LDL apo B	114 ± 4	75 ± 5*
HDL cholesterol	40 ± 4	48 ± 3*

* $p < 0.001$ vs placebo.
Values are expressed as mean ± standard error of the mean.
apo B = apolipoprotein B; other abbreviations as in Table I.
Adapted from *J Lipid Res.*[26]

TABLE IV Plasma Lipid and Lipoprotein Levels in 10 Patients with Primary Moderate Hypercholesterolemia

	Control (mg/dl)	Lovastatin + Colestipol (mg/dl)
Total cholesterol	260 ± 6	166 ± 5*
Triglycerides	107 ± 8	116 ± 2
LDL cholesterol	196 ± 6	101 ± 5*
LDL apo B	113 ± 4	68 ± 3*
HDL cholesterol	42 ± 4	49 ± 5

* $p < 0.02$ vs control.
Values are expressed as mean ± standard error of the mean.
Abbreviations as in Tables I and III.
Adapted from *JAMA.*[18]

who cannot tolerate bile acid sequestrants, reductase inhibitors can be tried as a single agent. The efficacy and safety of lovastatin in patients of this type have been documented in a multicenter trial[19] and in other studies.[20-24] As with FH heterozygotes, use of reductase inhibitors alone often fails to bring LDL cholesterol levels into the desirable range. Thus, if tolerated, at least moderate doses of bile acid sequestrants, i.e., 4 to 5 g twice daily, should be administered as a second drug when reductase inhibitors are used.

PRIMARY MODERATE HYPERCHOLESTEROLEMIA

This is the most common form of hypercholesterolemia in the general American public.[16,17] Total cholesterol levels typically are in the range of 240 to 300 mg/dl. These levels usually correspond to LDL cholesterol concentrations in the range of 160 to 220 mg/dl. Often dietary excesses add to the increase in LDL cholesterol levels; the major dietary factors that increase LDL concentrations are high intake of saturated fatty acids, cholesterol and total calories (obesity). While diet can be an important factor, a genetic predisposition to hypercholesterolemia frequently is present as well.[16] These genetic influences are not well defined. Some patients may have mild defects in LDL receptor metabolism; others may have abnormalities in the primary structure of apo B so that their LDL apo B binds poorly to LDL receptors; still others may have defects in VLDL metabolism, i.e., overproduction of VLDL particles or increased conversion of VLDL to LDL. The risk for CAD in patients with primary moderate hypercholesterolemia is at least twice that for patients whose serum cholesterol levels are below 200 mg/dl.[25] First-line therapy for elevated LDL concentrations is dietary modification, i.e., reduced intake of saturated fatty acids, cholesterol and total calories (if the patient is obese). However, if LDL cholesterol concentrations remain over 160 mg/dl despite maximal dietary therapy, consideration can be given to the possibility of using cholesterol reducing drugs.[17] The decision to use drugs depends largely on the presence or absence of other risk factors. Therefore, the discussion to follow divides patients into high- and low-risk categories.

High-risk patients: Factors that confer a high-risk status on patients with moderate hypercholesterolemia are the presence of atherosclerotic disease, i.e., CAD, peripheral vascular disease, carotid artery disease and cerebral vascular disease; a family history of premature CAD; smoking; hypertension; diabetes mellitus; low HDL cholesterol; and obesity.[17] Men are at higher risk; this factor belongs in the equation for deciding when to administer drug therapy. For high-risk patients with primary moderate hypercholesterolemia, particularly when 2 risk factors are present,[17] HMG CoA reductase inhibitors deserve to be high on the list for first-line therapy. Most patients of this type will respond to reductase inhibitors with a marked reduction in LDL cholesterol levels. This response is illustrated in a study performed in our laboratory[26] (Table III). Twelve patients with primary moderate hypercholesterolemia were treated with lovastatin (20 mg twice daily), and the results were compared with treatment with placebo. Total cholesterol levels declined 22% and LDL cholesterol 32% in those taking lovastatin therapy. LDL apo B levels also decreased 34%. In addition, HDL cholesterol concentrations increased 20%. For many patients with moderate hypercholesterolemia, LDL cholesterol decreased to the desirable range.

Even in this group, however, the combination of bile acid sequestrants and HMG CoA reductase inhibitors provides a still greater change in lipoprotein levels than lovastatin alone. Our investigations[18] have shown that this drug combination markedly reduces LDL levels in patients with primary moderate hypercholesterolemia (Table IV). In this study, 10 patients with primary moderate hypercholesterolemia were treated with lovastatin (20 mg twice daily) and colestipol (10 g twice daily). With combined drug therapy, total cholesterol decreased 36% and LDL cholesterol 48%. LDL apo B concentrations declined 40%. Because this drug combination is so highly efficacious, lower doses of both drugs often can be given, and an excellent response will still be obtained.[27] Lower doses reduce the danger of adverse effects from either drug. Despite the benefits of combined drug therapy, many patients prefer the ease of administration of reductase inhibitors used alone, and they choose not to add bile acid sequestrants. Still, combination drug therapy remains the preferred therapy because of its high efficacy.

Low-risk patients: In patients with no other risk factors, the presence of primary moderate hypercholesterolemia alone fails to justify HMG CoA reductase inhibitors as first-line therapy. Clinical trial data provide a strong reason to use a bile acid sequestrant as the drug of first

TABLE V Plasma Lipid and Lipoprotein Levels in Eight Patients with Familial Combined Hyperlipidemia with Type 4 Hyperlipoproteinemia

	Control (mg/dl)	Gemfibrozil Alone (mg/dl)	Gemfibrozil + Lovastatin (mg/dl)
Total cholesterol	261 ± 12	279 ± 13	197 ± 9*†
Triglycerides	381 ± 35	228 ± 25*	166 ± 12*
VLDL cholesterol	84 ± 10	51 ± 8*	29 ± 4*†
LDL cholesterol	146 ± 11	189 ± 8*	126 ± 7†
LDL apo B	133 ± 13	136 ± 10	95 ± 6*†
HDL cholesterol	31 ± 2	39 ± 2*	42 ± 2*

* p <0.05 vs control.
† p <0.005 vs gemfibrozil alone.
Values are expressed as mean ± standard error of the mean.
Abbreviations as in Tables I to III.
Adapted from *Ann Intern Med.*[31]

TABLE VI Plasma Lipid and Lipoprotein Levels in Nine Patients with Familial Combined Hyperlipidemia with Type 2B Hyperlipoproteinemia

	Control (mg/dl)	Gemfibrozil Alone (mg/dl)	Gemfibrozil + Lovastatin (mg/dl)
Total cholesterol	326 ± 13	290 ± 15*	232 ± 10*†
Triglycerides	293 ± 16	134 ± 8*	130 ± 8*
VLDL cholesterol	59 ± 7	21 ± 2*	18 ± 2*
LDL cholesterol	229 ± 14	221 ± 15	166 ± 10*†
LDL apo B	171 ± 15	140 ± 12*	113 ± 9*†
HDL cholesterol	38 ± 3	48 ± 5*	48 ± 5*

* p <0.005 vs control.
† p <0.005 vs gemfibrozil alone.
Values are expressed as mean ± standard error of the mean.
Abbreviations as in Tables I to III.
Adapted from *Ann Intern Med.*[31]

choice. The combination of dietary modification and moderate doses of a bile acid sequestrant effectively decreases LDL cholesterol in most patients, and high doses of a sequestrant or an HMG CoA reductase inhibitor generally are not necessary. Starting drug therapy for hypercholesterolemia presumably indicates the need for life-long therapy; therefore, further clinical trials documenting long-term safety, efficacy, and a low cost-benefit ratio are needed before committing otherwise low-risk patients with moderate hypercholesterolemia to HMG CoA reductase inhibitors. Dietary therapy needs to be stressed in such patients. If a hypocholesterolemic drug is considered necessary, use of a bile acid sequestrant in low to moderate doses should be the next step.

PRIMARY MIXED HYPERLIPIDEMIA

This condition consists of a combined elevation of serum total cholesterol and endogenous triglycerides (VLDL triglycerides), i.e., total cholesterol levels are about 240 mg/dl and serum triglycerides are in the range of 250 to 500 mg/dl. Multiple factors can contribute to the genesis of primary mixed hyperlipidemia; obesity is one of the most common. Some patients with mixed hyperlipidemia undoubtedly come under the category of familial combined hyperlipidemia,[28] which may be a single-gene disorder, whereas other patients may have inherited defects in the metabolism of both LDL and VLDL, and thus have a polygenic disorder. Patients with primary mixed hyperlipidemia are at increased risk for CAD,[29] perhaps to a greater extent than are those with primary moderate hypercholesterolemia who have the same level of total cholesterol. The elevation of triglycerides and the concomitant reduction of HDL cholesterol present in patients with mixed hyperlipidemia thus may impart an incremental risk for CAD beyond that caused by elevation of total cholesterol alone. Patients with mixed hyperlipidemia often have a marked increase in serum total apo B, and this abnormality, likewise, may indicate enhanced risk for CAD.

Because of the high risk for CAD associated with mixed hyperlipidemia, drug therapy usually can be justified. Gemfibrozil has recently been approved by the Food and Drug Administration for therapy of combined elevations of VLDL and LDL (type 2b hyperlipoproteinemia). Although gemfibrozil therapy definitely will reduce triglycerides and increase HDL levels with type 2b hyperlipoproteinemia, it usually does not reduce LDL cholesterol or total apo B levels.[30] Niacin therapy may produce a better response than gemfibrozil. Not only will niacin therapy lower VLDL and increase HDL levels, it will often reduce LDL levels. Unfortunately, niacin use frequently leads to a variety of adverse effects: gastrointestinal distress, flushing of skin and other skin reactions, hepatotoxicity, hyperuricemia and hyperglycemia. Thus, whereas niacin may be the drug of choice in primary mixed hyperlipidemia, many patients cannot tolerate it for long periods. Another approach is to administer combined drug therapy: gemfibrozil plus bile acid sequestrants[31] or niacin plus bile acid sequestrants.[32] Combined drug therapy is more efficacious for lipid reduction, but adverse effects are compounded.

In a recent study by East et al,[31] effects of lovastatin plus gemfibrozil vs gemfibrozil alone were examined in patients with familial combined hyperlipidemia, a form of primary mixed hyperlipidemia. The patients in this study had either type 4 hyperlipoproteinemia (increased triglycerides and "normal" LDL cholesterol) or type 2b hyperlipoproteinemia (increased triglycerides and increased LDL cholesterol). Results with type 4 hyperlipoproteinemia patients are shown in Table V. In 8 patients, gemfibrozil therapy alone significantly reduced plasma triglycerides and VLDL cholesterol and significantly increased HDL cholesterol. However, gemfibrozil used alone did not reduce total cholesterol, LDL cholesterol or LDL apo B levels. The combination of gemfibrozil plus lovastatin resulted in even greater reductions in plasma triglycerides and VLDL cholesterol and increases in HDL cholesterol; in addition, the combination therapy reduced total cholesterol, LDL cholesterol and LDL apo B levels.

Data for patients with familial combined hyperlipidemia with type 2b hyperlipoproteinemia are given in Table VI. A similar pattern was seen: Gemfibrozil therapy alone reduced VLDL and increased HDL. It did not reduce LDL cholesterol levels, but it did decrease LDL apo B significantly. Again, an even better result was

TABLE VII Plasma Lipid and Lipoprotein Levels in 12 Patients with Primary Mixed Hyperlipidemia

	Placebo (mg/dl)	Lovastatin (mg/dl)
Total cholesterol	285 ± 9	196 ± 7*
Total triglycerides	456 ± 36	308 ± 30*
VLDL cholesterol	105 ± 4	63 ± 7*
LDL cholesterol	152 ± 8	98 ± 6*
HDL cholesterol	28 ± 1	31 ± 2
Plasma apo B	149 ± 8	107 ± 6*

* $p < 0.01$ vs placebo.
Values are expressed as mean ± standard error of the mean.
Abbreviations as in Tables I to III.
Adapted from *Arch Intern Med*.[33]

TABLE VIII Plasma Lipid and Lipoprotein Levels in 16 Patients with Non-Insulin-Dependent Diabetes Mellitus

	Placebo (mg/dl)	Lovastatin (mg/dl)
Total cholesterol	233 ± 10	172 ± 7*
Triglycerides	308 ± 49	213 ± 24†
VLDL cholesterol	56 ± 11	33 ± 5‡
LDL cholesterol	140 ± 9	101 ± 6*
LDL apo B	108 ± 16	80 ± 16*
HDL cholesterol	37 ± 2	39 ± 2

* $p < 0.001$ vs placebo
† $p < 0.05$ vs placebo.
‡ $p < 0.01$ vs placebo.
Values are expressed as mean ± standard error of the mean.
Abbreviations as in Tables I to III.
Adapted from *N Engl J Med*.[36]

obtained with combined drug therapy. Unfortunately, this combination of agents has been reported to increase the risk for severe myopathy substantially, particularly in comparison with the risk involved in the use of either drug alone. Although toxicity data on this drug combination are limited, it appears that approximately 1 in 20 patients taking gemfibrozil plus lovastatin will develop severe myopathy. Thus, patients using these drugs in combination should be carefully monitored and therapy should be discontinued at the first sign of muscle discomfort or brown urine.

Because of the danger of myopathy with lovastatin plus gemfibrozil, another approach to primary mixed hyperlipidemia is lovastatin therapy alone. We have recently examined this mode of therapy in 12 patients with primary mixed hyperlipidemia (Table VII).[33] These patients had increased levels of both total cholesterol and total triglycerides. Treatment with lovastatin produced a decrease in total cholesterol of 34%, whereas triglycerides decreased 32%. Levels of VLDL cholesterol and LDL cholesterol declined 40 and 36%, respectively, and plasma apo B levels decreased 28%. HDL cholesterol concentrations did not increase. Thus, lovastatin therapy was most effective in decreasing apo B-containing lipoproteins and had little effect on HDL cholesterol. Nonetheless, total cholesterol (and LDL)/HDL cholesterol ratios were markedly reduced by lovastatin therapy alone. Although the use of lovastatin alone did not normalize HDL cholesterol levels, its favorable effects on apo B-containing lipoproteins makes it a reasonable alternative to nicotinic acid and probably superior to gemfibrozil in patients with primary mixed hyperlipidemia.

DIABETIC DYSLIPIDEMIA

CAD is the major killer of diabetic patients, and whereas several factors in diabetic patients may increase coronary risk, secondary dyslipidemia almost certainly is an important contributor.[34] Patients with non-insulin-dependent diabetes mellitus (NIDDM) are particularly prone to a variety of lipoprotein abnormalities. The pattern of diabetic dyslipidemia often is that of a mixed hyperlipidemia: increased VLDL cholesterol and VLDL triglyceride levels, increased LDL and reduced HDL cholesterol. Not all patients with NIDDM have distinctly increased LDL cholesterol levels, but even those who do not, frequently have abnormalities in LDL composition and metabolism.[34] Furthermore, even mild elevations of LDL cholesterol may contribute significantly to increased CAD risk in diabetic patients. For example, Caucasian diabetic patients who have borderline high cholesterol levels have much higher rates of CAD than Pima Indians who have cholesterol concentrations in the desirable range.[34] Because of the atherogenic potential of diabetic dyslipidemia, drug therapy for modification of lipid levels in patients with NIDDM is worthy of consideration.

The most obvious drug for treatment of diabetic dyslipidemia is niacin. It lowers serum levels of VLDL and LDL and increases HDL. Unfortunately, niacin often raises serum glucose which is especially unfavorable in diabetic patients. An increase in uric acid levels is another undesirable response to niacin therapy. Because of its adverse effects, therefore, niacin probably has limited use in the treatment of diabetic dyslipidemia. Gemfibrozil will reduce triglyceride levels of patients with NIDDM, but at the same time will usually increase LDL cholesterol.[35] Bile acid sequestrants have not been tested extensively in diabetic patients, but these drugs have 2 potential drawbacks. They often cause constipation, which may be a particular problem for diabetic patients, and they tend to increase triglyceride levels. Because of these possible problems, bile acid sequestrants like nicotinic acid probably will be of limited usefulness in patients with NIDDM.

Another type of drug that may be considered for diabetic patients is an HMG CoA reductase inhibitor. To test this possibility, we performed a study to determine the effectiveness and safety of lovastatin in a series of patients with NIDDM.[36] The results showed a favorable response (Table VIII). Levels of VLDL triglycerides and cholesterol decreased significantly in these patients. Lovastatin therapy was particularly effective in reducing LDL cholesterol and LDL apo B concentrations. On the other hand, lovastatin therapy did not significantly increase HDL cholesterol levels. Use of lovastatin, nonetheless, induced an overall favorable response in the lipoprotein pattern of these patients. This occurred without development of significant adverse effects over the short duration of therapy. In our view, therefore, HMG CoA reductase inhibitors may be particularly useful for pre-

TABLE IX Plasma Lipid and Lipoprotein Levels in 22 Normolipidemic Patients with Hypoalphalipoproteinemia

	Placebo (mg/dl)	Gemfibrozil (mg/dl)
Total cholesterol	198 ± 6	184 ± 6*
Triglycerides	187 ± 20	118 ± 10*
VLDL cholesterol	39 ± 4	25 ± 2*
LDL cholesterol	128 ± 5	125 ± 5
LDL apo B	112 ± 6	101 ± 5
HDL cholesterol	30 ± 1	33 ± 1*

* $p < 0.0083$ vs placebo.
Values are expressed as mean ± standard error of the mean.
Abbreviations as in Tables I to III.
Adapted from *JAMA*.[41]

TABLE X Plasma Lipid and Lipoprotein Levels in 22 Normolipidemic Patients with Hypoalphalipoproteinemia

	Placebo (mg/dl)	Lovastatin (mg/dl)
Total cholesterol	192 ± 7	138 ± 5*
Triglycerides	181 ± 13	140 ± 9*
VLDL cholesterol	39 ± 4	24 ± 2*
LDL cholesterol	124 ± 6	82 ± 5*
LDL apo B	104 ± 5	79 ± 4*
HDL cholesterol	29 ± 1	32 ± 1*

* $p < 0.0083$ vs placebo.
Values are expressed as mean ± standard error of the mean.
Abbreviations as in Tables I to III.
Adapted from *JAMA*.[41]

vention of CAD by modifying serum lipoproteins in patients with NIDDM.

In another study,[35] we examined the effect of the combination of lovastatin plus gemfibrozil in patients with NIDDM. As in patients with familial combined hyperlipidemia, the results were highly favorable. As indicated before, the increased danger of severe myopathy probably precludes routine use of lovastatin and gemfibrozil in combined drug therapy.

HYPERLIPIDEMIA OF THE NEPHROTIC SYNDROME

Another secondary form of hyperlipidemia is the nephrotic syndrome. In the nephrotic syndrome, levels of LDL cholesterol often are greatly increased. This effect is considered by many investigators to be secondary to overproduction of apo B-containing lipoproteins by the liver, apparently a response to loss of protein in the urine. Because hepatic synthesis of cholesterol appears to be increased as well, there may be a secondary suppression of LDL receptor activity. The combination of overproduction of lipoproteins and reduced LDL receptor activity may account for the marked hypercholesterolemia observed in many nephrotic patients. Many patients with the nephrotic syndrome manifest hypertriglyceridemia in addition to elevated LDL cholesterol. Again, 2 mechanisms may contribute to high triglyceride concentrations. First, there may be hepatic overproduction of VLDL triglycerides; second, the lipolysis of triglyceride-rich lipoproteins appears to be impaired. The latter alteration may be due to reduced activity of either lipoprotein lipase or hepatic triglyceride lipase, or both. There is increasing evidence that the hyperlipidemia of the nephrotic syndrome predisposes patients to CAD, provided the hyperlipidemia is of prolonged duration.

We recently reported that lovastatin is highly effective in reducing plasma lipids in nephrotic patients.[37] In our study, 3 patients with marked hypercholesterolemia were studied for alterations in plasma lipids and lipoproteins and for changes in kinetic parameters of apo B-containing lipoproteins. Lovastatin therapy produced a marked reduction in both total cholesterol and total triglyceride levels in these patients. Reductions extended to both VLDL cholesterol and LDL cholesterol; furthermore, HDL cholesterol levels, which were reduced in the control period, increased strikingly with lovastatin therapy. More recently, other workers[38,39] have reported on effects of HMG CoA reductase inhibitors on hyperlipidemia of the nephrotic syndrome, and similar results were obtained. Therefore, it appears as though reductase inhibitors will effectively reduce cholesterol concentrations in nephrotic hypercholesterolemia. However, cholesterol levels generally are not reduced to the normal levels with reductase inhibitor therapy alone, and nephrotic patients may benefit from combination therapy of reductase inhibitors and bile acid sequestrants, as observed for FH heterozygotes (Tables I and II). To date, however, this combination has not been tried.

HYPOALPHALIPOPROTEINEMIA

Finally, another condition in which risk for CAD is raised, is a low HDL cholesterol concentration. A heightened risk for CAD apparently exists even when levels of total cholesterol and triglycerides are not increased. In fact, one of the most common lipoprotein patterns observed in patients with CAD is a low HDL cholesterol concentration with normal plasma lipids. The mechanisms for reduced HDL cholesterol have not been determined in these patients. Whether the defect lies in the metabolism of triglycerides or apo AI remains to be clarified. Certainly, a reduced HDL cholesterol can be secondary to other factors, e.g., obesity, lack of exercise, cigarette smoking, or other drugs (such as β-adrenergic blocking agents and androgenic hormones). When these causes exist, their correction will increase HDL concentrations to the desirable range. In other patients, however, a low HDL concentration persists despite modification of life style; for such patients, consideration can be given to use of drugs that increase HDL levels.

Nicotinic acid may be the drug of first choice for treatment of isolated hypoalphalipoproteinemia. This drug probably increases HDL levels better than any other. Unfortunately, it also is accompanied by a variety of adverse effects, and many patients are not able to tolerate it for prolonged periods. For this reason, consideration must be given to the use of other agents. Two such possibilities are gemfibrozil and lovastatin. Many investigators believe that gemfibrozil is a good HDL-raising drug. In the Helsinki Heart Study,[40] gemfibrozil given to patients with hypercholesterolemia resulted in a decreased risk for CAD, and part of this beneficial effect was attributed to an induced increase in HDL cholesterol concentrations. Another drug that has been reported to increase HDL levels modestly is lovastatin. For this reason, we performed a study to compare gemfibrozil therapy with lovastatin therapy in 22 men with low HDL cholesterol and normal plasma lipids.[41]

The effects of gemfibrozil therapy in these patients are listed in Table IX. Treatment with the drug caused a modest reduction in plasma total cholesterol and a moderate decrease in triglyceride levels. VLDL cholesterol concentrations significantly decreased, but no changes were noted for LDL cholesterol or LDL apo B. HDL cholesterol concentrations increased modestly, i.e., about 10%. Results for lovastatin therapy are given in Table X. Although lovastatin therapy reduced plasma triglyceride levels less than gemfibrozil, lovastatin therapy had about the same effect on VLDL cholesterol levels. Lovastatin therapy caused much more marked reductions in total cholesterol, LDL cholesterol and LDL apo B concentrations. Moreover, lovastatin increased HDL cholesterol approximately 10%, the same as gemfibrozil. Thus, overall, lovastatin therapy produced a much better response in plasma lipoproteins than did gemfibrozil therapy. For this reason, we suggest that lovastatin is a better alternative to nicotinic acid for treatment of hypoalphalipoproteinemia with normal plasma lipids than is gemfibrozil.

CONCLUSIONS

The usefulness of HMG CoA reductase inhibitors for treatment of severe hypercholesterolemia is well established and fully justified. The same is true for treatment of patients with moderate hypercholesterolemia who otherwise are at high risk for CAD. For those with moderate elevations of LDL cholesterol who are not at high risk, it may be prudent to use maximal dietary therapy, or at most, to use bile acid sequestrants with dietary therapy. However, as shown by several investigations from our laboratory, HMG CoA reductase inhibitors may be useful drugs for treatment of other forms of hyperlipidemia. These include mixed (combined) hyperlipidemia, diabetic dyslipidemia, nephrotic dyslipidemia and hypoalphalipoproteinemia. Although our studies do not provide proof that reductase inhibitors are effective in reducing risk of CAD in these conditions, or that they are entirely safe for long-term use, our data are highly suggestive of benefit. Future clinical trials of drug therapy for these conditions should use HMG CoA reductase inhibitors as one arm of the study. In addition, among high-risk patients with one of these various dyslipidemias, consideration can be given to using a reductase inhibitor at the current time.

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Lovastatin and Simvastatin Prevention Studies

Peter H. Jones, MD

There is substantial evidence that drug treatment of hypercholesterolemia in patients without known coronary artery disease (CAD) can reduce fatal and nonfatal CAD events. Two trials, the Lipid Research Clinics Coronary Primary Prevention Trial and the Helsinki Heart Study used cholestyramine and gemfibrozil, respectively, to alter lipoprotein levels; their demonstrated efficacy and safety have led to their widespread use in hyperlipidemic patients.

Recently, a new class of hypolipidemic agents has been shown to be extremely effective in lowering total and low-density lipoprotein cholesterol levels. These drugs, including lovastatin and simvastatin, competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme of intracellular cholesterol synthesis. Results of safety and efficacy studies suggest that they may be valuable first-line treatment options for high-risk hypercholesterolemic patients.

Two long-term clinical trials are planned with lovastatin and simvastatin. In the United States, lovastatin will be used in a double-blind, placebo-controlled, primary prevention trial involving 8,000 patients without clinical evidence of CAD, slight to moderate elevations of total cholesterol, and low- and high-density lipoprotein cholesterol to establish whether 5 years of treatment will decrease the rate of fatal CAD or nonfatal myocardial infarction. A Scandinavian study of 4,000 patients with ischemic heart disease and hypercholesterolemia will determine if simvastatin will improve total survival and reduce fatal or nonfatal myocardial infarction and sudden death for at least 3 years. These study designs will be discussed and compared with other studies, and the expected impact on CAD event rates presented.

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The introduction of lovastatin in the United States in 1987, and of simvastatin in Western Europe and Scandinavia in 1989, marked a new era in the management of hypercholesterolemia. These medications are the first in a class of drugs that competitively inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase that controls intracellular cholesterol synthesis. The combination of excellent patient tolerance, low side-effect profiles, and pronounced efficacy in reducing low-density lipoprotein (LDL) cholesterol have made them popular options with physicians for the primary and secondary prevention of coronary artery disease (CAD) due to hypercholesterolemia. On the other hand, the landmark results of the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),[1] the Helsinki Heart Study (HHS),[2] and the long-term mortality report of the Coronary Drug Project[3] have led many lipid experts in the United States to recommend cholestyramine, niacin and gemfibrozil as first-line treatment options for patients at risk for CAD. In an effort to confirm the results of these studies, several important trials with lovastatin and simvastatin are planned that should directly address their safety and efficacy in both the primary and secondary prevention of CAD. The details of 2 of these trials, the Lovastatin Primary Prevention Trial (LPPT) and the Scandinavian Simvastatin Survival Study, will be discussed and the worldwide clinical experience with simvastatin will be reviewed.

SIMVASTATIN CLINICAL EXPERIENCE

Simvastatin is closely related to lovastatin in structure, differing only in the addition of 1 methyl group (Fig. 1). In fact, the naturally occurring lovastatin, a metabolite of *Aspergillus terreus*, serves as the base for synthetically derived simvastatin. Both drugs are ingested in the inactive closed lactone ring form, and are converted to the active open B-hydroxy form by the liver. The pharmacokinetics of the 2 drugs are very similar[4]; about 30% of the oral dose is absorbed and over 90% of that amount is extracted by the liver on first pass. Less than 5% of the active form of the drugs reaches the systemic circulation. Elimination is primarily through the gastrointestinal tract, through a combination of nonabsorption and biliary excretion. Urinary excretion accounts for less than 10% of the total elimination. Both lovastatin and simvastatin have structural components that are analogs of HMG CoA, and as a consequence, will competitively inhibit this rate-limiting enzyme. This action will result in a reduction of intracellular cholesterol synthesis, and an increase in cellular membrane LDL receptor expression. In vitro studies have confirmed a high affinity of lovasta-

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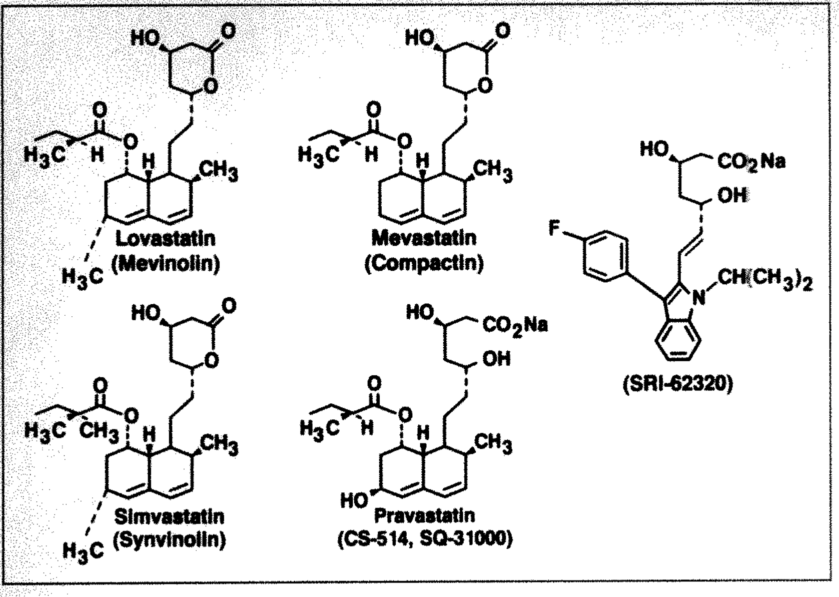

FIGURE 1. Structure of various 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

tin for HMG CoA reductase, whereas simvastatin appears to be twice as potent as lovastatin in such affinity tests. Clinical efficacy studies on total and LDL cholesterol reduction, discussed later, generally confirm that simvastatin is approximately twice as potent in milligram-to-milligram comparisons with lovastatin.

Approximately 10,700 patients worldwide have been studied with simvastatin as of early 1989, and about 1,200 of these have taken the drug for at least 2 years. The side-effect profile is quite similar to that of lovastatin, confined to reversible hepatic transaminase elevations (<2.5%), myositis (<2%) and gastrointestinal complaints (nausea, diarrhea). Thus far, no evidence has linked lovastatin and simvastatin with the formation of lens opacities. Although the precise mechanism of myositis attributed to the HMG CoA reductase inhibitors is unknown, an interaction of several drugs with the reductase inhibitors appears to increase the risk. Therefore, the concomitant use of cyclosporine, fibric acid derivatives, niacin, or erythromycin with lovastatin and simvastatin is discouraged until further studies can clarify the risk-to-benefit ratio.

Studies examining the efficacy of simvastatin in short-term administration are summarized in Table I.[5-11] Various dosing regimens of 2.5 to 80 mg/day were employed in hypercholesterolemic subjects. Nakaya and Goto[7] and Bocanegra et al[10] show that administration of simvastatin, 2.5 to 10 mg/day, can achieve 22 to 26% reductions in LDL cholesterol levels, suggesting an efficacy similar to that of lovastatin at doses of 20 mg/day. Bocanegra et al[10] also demonstrated that 10 to 20 mg/day of simvastatin achieved LDL cholesterol reductions (34%) similar to those achieved with 40 mg/day of lovastatin. Reports from long-term simvastatin efficacy studies (Table II) help to confirm the clinical impression that simvastatin is approximately twice as potent as lovastatin in milligram-to-milligram doses.[12-16]

Simvastatin has been compared directly to other hypolipidemic medications in terms of efficacy. The Simvastatin Multicenter Study Group II[17] was a 12-week, randomized, double-blind comparison of simvastatin (20 and 40 mg) and probucol (1,000 mg/day). The principal results, listed in Table III, demonstrate the considerable advantage of simvastatin in LDL cholesterol and apolipoprotein B reductions compared with probucol. Adverse events in this short-term study were small and not different among the 3 treatment groups. Gemfibrozil was compared with simvastatin in a large number of subjects by Bocanegra et al.[10] This randomized, double-blind, 12-week trial in 290 patients with primary hypercholesterol-

TABLE I Simvastatin—Short-Term Studies (Less than Six Months)

			% Change in Lipid Parameters				
Study	No. of Pts.	Dose (mg)	TC	LDL	HDL	Tg	Apo B
Mol et al[5]	11	40–80	−32 to −36	−37 to −42	−9 to 21	−11 to −34	
Weisweiler[6]	10	40	−35	−44			−38
Nakaya and Goto[7]	241	2.5–5	−17	−22	+8		−16
Kuhn et al[8]	19	2.5–20	−10 to −35	−19 to −49	0 to +9	−15	
Hayden et al[9]	21	10–40	−25 to −30	−38 to −42	+2 to +9		
Bocanegra et al[10]	68	5–10	−21	−26	+7		
	78	10–20	−34	−34	+9		
Schulzeck et al[11]	16	20–40	−30	−37		−14	−38

Apo B = apolipoprotein B; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; TC = total cholesterol; Tg = triglycerides.

TABLE II Simvastatin—Long-Term Studies (More than Six Months)

Study	No. of Pts.	Dose (mg)	% Change in Lipid Parameters TC	LDL	HDL	Tg	Apo B
Uno et al[12]	20	2.5–10	−23		+13	−31	−20
Ojala et al[13]	10	10–20		−33			−26
Miller et al[14]	34	20	−29	−35	+16		
		40	−32	−38			
Lintott et al[15]	24	40	−31	−41	+12		
Reisen and Mordasini[16]	8	40	−24		+20	−12	−20

Abbreviations as in Table I.

emia stratified each subject according to his or her LDL cholesterol level. Stratum I had LDL cholesterol levels ≥4.3 mm/liter (170 mg/dl) but <5 mm/liter (195 mg/dl), and stratum II had levels >5 mm/liter. The results are listed in Table IV. It is apparent that simvastatin, in doses of 10 to 20 mg/day, is superior to gemfibrozil in total and LDL cholesterol reduction. The incidences of adverse events attributable to simvastatin were minimal. Hepatic transaminase (alanine aminotransferase and aspartate aminotransferase) elevations over 3 times the upper limit of normal were seen in <2% of patients, and were reversible. Elevations in creatine kinase greater than 3 times the upper limit of normal were seen in 2.5% of patients; however, none of these patients was symptomatic or was considered to have active myositis.

PROPOSED CLINICAL TRIALS

As mentioned previously, there are 2 large-scale primary prevention drug trials that have demonstrated very favorable reductions in CAD morbidity and mortality when cholesterol levels are reduced in high-risk men. In the LRC-CPPT, an 8 to 9% reduction in total cholesterol by cholestyramine produced a 19% decline in CAD events over 7.4 years.[1] In the HHS, when gemfibrozil produced a 9% decrease in total cholesterol plus a 10% increase in HDL cholesterol, there was a 34% decline in definite CAD events over 5 years.[2] Both of these landmark trials included high-risk men, aged 35 to 59 years with elevated LDL cholesterol levels (average 215 mg/dl in the CPPT, 189 mg/dl in the HHS). The HHS was the first trial to underscore the importance of HDL cholesterol to CAD risk. The subgroup of men with HDL levels less than 45 mg/dl who had type IIb lipoprotein phenotype and received gemfibrozil, demonstrated the greatest reduction in CAD events.[18] Cox proportional hazards analysis of the HHS has suggested that the increase in HDL cholesterol contributed significantly to the overall reduction in CAD seen in the trial.

There has been some criticism of these studies, however. The fact that the CPPT results could only reach statistical significance at the 0.05 level by use of the single-tailed Student's *t* test has weakened its impact. The use of cholestyramine in the CPPT was associated with significant compliance problems, and has brought into question the usefulness of this drug in long-term prevention strategies. No definite conclusions concerning treatment recommendations for women or patients older than 60 years could be reached. Although CAD mortality was reduced, there was no benefit of drug treatment on total mortality. Addressing these criticisms is part of the rationale for organizing the largest primary drug prevention trial of CAD ever attempted.

The lovastatin primary prevention trial, to be referred to as the Air Force Coronary Atherosclerosis Prevention Study (AFCAPS), is a randomized, double-blind, placebo-controlled trial involving 8,000 patients in 2 military hospitals in San Antonio, Texas. The primary objective of the study is to investigate whether treatment with lovastatin in patients without clinical evidence of CAD, but with slight to moderately elevated cholesterol and low HDL cholesterol levels, will decrease the rate of nonfatal myocardial infarction or fatal CAD over at least 5 years. Secondary objectives are to determine whether lovastatin will decrease the rates of hospitalization due to: CAD and

TABLE III Mean Lipid Levels (mg/dl) (Baseline and Treatment) in Simvastatin Multicenter Study Group II

	Baseline	Week 12 Simvastatin (20 mg)	Simvastatin (40 mg)	Probucol
Patients	243	82	80	81
Total cholesterol	323	240 (−26%)	216 (−33%)	285 (−12%)
LDL cholesterol	251	168 (−33%)	142 (−43%)	227 (−10%)
HDL cholesterol	45	50 (+11%)	50 (+11%)	33 (−27%)
Apo B	203	137 (−33%)	116 (−43%)	162 (−21%)
Triglycerides	158	120 (−24%)	121 (−23%)	152 (−4%)

Abbreviations as in Table I.
Adapted from Am J Cardiol.[17]

TABLE IV Simvastatin and Gemfibrozil Effects on Plasma Lipids in Primary Hypercholesterolemia

Drug (dose per day)	No. of Pts.	Mean % Change TC	LDL	HDL
Simvastatin (stratum I) 5–10 mg	68	−21	−26	+7
Simvastatin (stratum II) 10–20 mg	78	−27	−34	+9
Gemfibrozil (stratum I) 1,200 mg	69	−15	−18	+17
Gemfibrozil (stratum II) 1,200 mg	75	−15	−17	+16

Stratum I LDL cholesterol ≥4.3 and < 5 mm/liter.
Stratum II LDL cholesterol ≥5 mm/liter.
Abbreviations as in Table I.

other atherosclerotic vascular disease, the need for coronary bypass grafting and percutaneous transluminal coronary angioplasty, the development of angina and positive electrocardiographic changes, and total mortality. The patient population will include men (aged 45 to 70 years) and women (aged 55 to 70 years) who are free of clinically evident CAD and meet the following lipid criteria: total cholesterol 180 to 240 mg/dl (4.65 to 6.2 mm/liter), LDL cholesterol 130 to 190 mg/dl (3.36 to 4.91 mm/liter), HDL cholesterol ≤45 mg/dl (<1.16 mm/liter) and triglycerides ≤400 mg/dl (≤4.54 mm/liter). These lipid entry criteria are based on the mean of 2 successive determinations after patients have been eating a lipid-lowering diet for at least 8 weeks (American Heart Association phase I diet). The active treatment phase will have all patients randomized into 2 groups: group I — lovastatin 20 mg/day as an evening dose; group II — placebo once a day as an evening dose. The goal of therapy in the study is to reduce serum LDL cholesterol as much as possible to ≤110 mg/dl (≤2.84 mm/liter). After 12 weeks of therapy, all patients whose serum LDL cholesterol is ≥110 mg/dl at 2 successive measurements will have their medication increased to 2 doses a day. A central laboratory will have computer-generated instructions for dose changes which should maintain the blind during the study.

The sample size estimation and power of the study assumes a 4% cumulative total CAD event rate in the placebo group. To achieve a power of 90% at an α of 0.05 (2-sided) for detecting a 33% reduction in the total CAD event rate in the lovastatin-treated group, the sample size needs to be approximately 8,000 subjects. Based on these assumptions, the expected total number of CAD events is estimated to be 270 in this study. All of the patients will be followed until the last randomized patient has completed 5 years of treatment or until the expected 270 CAD events are recorded, whichever comes last. The final analysis of the trial will be on the "intention-to-treat" format for all end points.

There are several unique aspects of the AFCAPS that have not been addressed in previous primary prevention studies. First, the patient population will include subjects up to age 70 years at the time of randomization. This means a substantial number of subjects could be between 65 and 75 years at the end of the study. As a result, analysis of these patients may permit an examination of the benefits of primary drug prevention for CAD among older age groups. The study also allows women of postmenopausal age to enter. If their numbers are sufficiently great, this would be the first analysis of the benefits of primary drug prevention in women. In direct contrast with the CPPT and HHS, the AFCAPS is including patients with more modest elevations of total and LDL cholesterol levels, which should help to address the benefits of primary treatment in the range of hypercholesterolemia (180 to 240 mg/dl) most often observed in patients who develop CAD in the United States.

The study has targeted a goal of therapy, based on LDL cholesterol, that is to be achieved in the treatment group. The chosen goal of LDL cholesterol ≤110 mg/dl has not uniformly been achieved in a primary prevention study. The AFCAPS Steering Committee recommended goal-oriented therapy because it reflects the basic drug treatment philosophy of the National Cholesterol Education Program Expert Panel, which has recommended using LDL cholesterol cutpoints as goals of hypercholesterolemic therapy.[19] Last, the AFCAPS will terminate at 270 expected primary end points, not on a definite calendar time. This feature will ensure that the study reaches sufficient significance to detect or not detect a benefit of treatment.

The Scandinavian Simvastatin Survival Study is a secondary prevention trial that will involve approximately 4,000 patients in 100 centers throughout 4 Scandinavian countries. The primary objective is to investigate whether treatment with simvastatin in patients with ischemic heart disease and hypercholesterolemia will improve overall survival during at least a 3-year period. Secondary objectives are to determine whether simvastatin treatment will reduce fatal or nonfatal myocardial infarction and sudden death. The randomized, double-blind, placebo-controlled study criteria require patients to be men and women aged 35 to 70 years with either a 3-month or longer history of angina pectoris or a myocardial infarction at least 6 months before entry. They must also have a fasting total cholesterol level between 5.5 mm/liter (213 mg/dl) and 8.0 mm/liter (310 mg/dl) after 8 weeks of dietary treatment. Patients with a typical history of angina must also have 1 of the following objective evidences of CAD: an electrocardiogram with ischemic changes during an episode of typical chest pain, an exercise electrocardiogram showing definite ischemia, or at least 1 coronary artery with ≥70% stenosis detected by angiography. Patients with a myocardial infarction (by classic criteria) must also be classified as low risk if there is no evidence of congestive heart failure, no evidence of chronic atrial fibrillation or flutter, and no need for chronic antiarrhythmic medication. Active treatment will include patients randomized to either simvastatin 20 mg as an evening dose or simvastatin-placebo. After 12 weeks, patients with a total cholesterol greater than 5.2 mm/liter (200 mg/dl) will have their medication increased to 1 tablet twice a day. Any patient who has a total cholesterol remaining above 9.0 mm/liter (350 mg/dl) at week 24 will be withdrawn from the study, and any patient who has a total cholesterol below 3.0 mm/liter (120 mg/dl) will have his or her medication dose cut in half. It is desired that patients in the simvastatin-treated group have their total cholesterol below 5.2 mm/liter, and as close to 3.0 mm/liter as possible for the length of the study. The time course of treatment is to be at least 3 years or until 380 expected deaths are observed, whichever comes last. There is an early stopping rule using group-sequential design, with analysis at 180 deaths, 300 deaths and 380 expected deaths.

The estimation of sample size and power assumes that the annual total mortality rate is 10% in the placebo patients with stable angina, and 12% in patients with low-risk myocardial infarctions. The sample size needed, therefore, is approximately 3,600 patients to reach a power of 95% at an α of 0.05 for detecting an overall 30% reduction in mortality in the active drug treatment group. The final analysis will be based on the "intention-to-treat" approach for the primary end points.

The Scandinavian Simvastatin Survival Study is unique for several reasons. First, it is the largest secondary prevention trial to be attempted. The Coronary Drug Project had 1,119 men randomized to niacin and the Stockholm Ischemic Heart Disease Study[20] had only 279 patients randomized to treatment (niacin and clofibrate). Both of these studies showed significant reduction in total mortality, one occurring at 5 years (Stockholm) and the other at 15 years.[3,20] It is expected that the simvastatin study, because of its size, will take approximately 3 years to demonstrate this benefit. As with the AFCAPS, the simvastatin study will include women. It also has defined treatment goals for the active drug group, based on total cholesterol. The patients defined for entry have total cholesterol levels that fall in the range that is seen most often in patients with CAD in this country (215 to 310 mg/dl). A positive result favoring treatment in this study would then be directly applicable to almost all patients who have objective evidence of CAD.

DISCUSSION

The cause and effect relationship between blood lipid abnormalities (predominately high LDL cholesterol) and the development of coronary atherosclerotic disease has been demonstrated beyond reasonable doubt. Both primary (LRC-CPPT, HHS)[13] and secondary (Coronary Drug Project, Stockholm Ischemic Heart Disease Study)[3,20] drug prevention studies have provided the best data to support the lipid hypothesis. However, these studies were limited in their scope; they enrolled mostly middle-aged men with very high total cholesterol levels, and did not firmly establish how aggressively to treat patients at risk. The inclusion of older patient groups and women, the use of more moderate cholesterol elevations as entry criteria, and the use of goal-oriented cholesterol treatment in both the AFCAPS and the Scandinavian Simvastatin Survival Study should provide extremely valuable, clinically relevant information in the management of cholesterol abnormalities for the primary and secondary prevention of CAD.

At the very least, final results favoring treatment in these studies should strengthen the national effort to detect and modify elevated blood cholesterol levels in adults in order to reduce the incidence of the number one cause of death in the United States.

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Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Design and Patient Characteristics of a Double-Blind, Placebo-Controlled Study in Patients with Moderate Hypercholesterolemia

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The randomized, double-blind, placebo-controlled trial described in this report was undertaken to clarify the dose-response relation of lovastatin therapy to lipid-modifying efficacy (lipid/lipoprotein modification) and drug-related adverse events in a population with moderately elevated fasting plasma total cholesterol (240 to 300 mg/dl) and low-density lipoprotein cholesterol (≥160 mg/dl). Men or women (postmenopausal or surgically sterile), aged 18 to 70 years, were entered into the trial with minimal exclusion criteria. After 4 to 6 weeks of an American Heart Association phase I diet or a more stringent diet, 8,245 patients from 362 sites were randomized to 1 of 5 parallel diet and drug treatment groups: placebo (n = 1,663) or lovastatin, 20 mg (n = 1,642) and 40 mg (n = 1,645) with the evening meal, and 20 mg (n = 1,646) or 40 mg twice daily (n = 1,649). The regimen of diet and lovastatin (or placebo) was followed for 48 weeks. The 5 treatment groups were similar at baseline. The total cohort had the following characteristics: 59% were men (mean age 56 years); 92% were white; 59% had completed at least 1 year of education beyond high school; 57% had a history of cardiovascular and associated disease; 40% had a history of hypertension; and 29% had coronary artery disease. Health habits were similar among groups, with 18% of patients reporting cigarette smoking, 14% reporting that they consume >1 alcoholic beverage daily and 67% reporting no strenuous exercise. Mean lipid/lipoprotein levels were also similar among groups, with the following average levels: total cholesterol (258 mg/dl), low-density lipoprotein cholesterol (180 mg/dl), high-density lipoprotein cholesterol (45 mg/dl) and triglycerides (median = 155 mg/dl). The large size of this trial, its placebo-controlled, double-blind design and the similarity of treatment groups at baseline should allow clear documentation of the long-term effects of lovastatin treatment and generalization of the results to a substantial portion of patients who may be candidates for lipid-modifying therapy.

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Lovastatin is a potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase.[1] This inhibition results in reduced synthesis of hepatic cholesterol, from acetate, up-regulation of hepatic low-density lipoprotein (LDL) receptors and subsequent reductions in the plasma concentration of LDL cholesterol.[2] In addition to the observed dose-dependent reductions in mean LDL cholesterol levels of 17 to 42%, reduced levels of triglycerides (14 to 27%) and increased levels of high-density lipoprotein (HDL) cholesterol (8 to 13%) are also observed with lovastatin therapy.[3,4]

In large, multicenter, controlled, double-blind clinical trials of short duration, lovastatin was well tolerated with only rare serious drug-attributable adverse experiences.[5-8] During extended open-label treatment, 2 successive elevations in serum transaminase levels were reported in 1.9% of adult patients who received lovastatin for at least 1 year.[9] Myopathy (defined arbitrarily as elevations in creatine phosphokinase [CPK] exceeding 10 times the upper limit of normal, with associated muscle symptoms) was reported in 0.5% of patients.[9] New lens opacities were also observed, but the causal relation to lovastatin has not been established.[9,10] Conclusions relating lovastatin's relation to adverse experiences have been uncertain because (1) extended treatment periods were unblinded and uncontrolled, (2) some patients concomi-

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tantly received other lipid-lowering drugs as well as potentially toxic agents (e.g., immunosuppressants), (3) patients were recruited from specialized lipid research and treatment centers and had severe hypercholesterolemia (total cholesterol ≥300 mg/dl), and (4) almost all of these patients (72%) received 80 mg/day of lovastatin (the maximal recommended daily dose).

The multicenter trial described herein was undertaken to clarify dose-response relation of lovastatin therapy to its lipid/lipoprotein-modifying efficacy and treatment-related adverse events in a population with moderately elevated plasma LDL and total cholesterol levels. Important attributes of this study include (1) the selection of patients with primary type II hyperlipoproteinemia (hypercholesterolemia) with moderate elevations in LDL cholesterol, (2) recruitment from a diversity of primary health care sources, (3) randomization to fixed treatment regimens of lovastatin or placebo for a 48-week treatment period, (4) exclusion of concomitant lipid-lowering agents, and (5) a sample size large enough to detect the dose-response relation for relatively rare events such as 2 successive serum transaminase elevations.

This report describes the study objectives, design, methods and patient cohort at baseline and evaluates the success of the randomization process.

METHODS

Patients: Participating centers recruited men or women with primary type II hyperlipoproteinemia (hypercholesterolemia), defined as fasting plasma total cholesterol level of 240 to 300 mg/dl, LDL cholesterol level ≥160 mg/dl and triglyceride level <350 mg/dl.

The exclusion criteria were selected to approximate conditions in medical practice. The following were excluded: (1) premenopausal women (unless surgically sterilized); (2) patients older than 70 or younger than 18 years; (3) patients with primary types of hyperlipoproteinemia characterized by elevations in lipids other than LDL cholesterol; and (4) those with secondary causes of hyperlipoproteinemia (e.g., hypothyroidism, uncontrolled diabetes, nephrotic syndrome). To minimize confusion in assessing the etiology of potential adverse events, patients with the following were also excluded: impaired hepatic function (or liver function test results >10% above the upper limit of the normal range); baseline CPK >1,000 U/liter; current or recent history of drug or alcohol abuse, defined as the consumption of >14 alcoholic drinks each week; concurrent use of other lipid-lowering or investigational drugs; or other significant or unstable medical conditions or concomitant therapies that, in the investigator's opinion, could confound the results of the study or pose a risk to the patient (e.g., symptoms of unstable coronary insufficiency; ventricular ectopic beats >5/min; coupling or R-on-T phenomenon; or having had a myocardial infarction, coronary artery bypass graft or coronary angioplasty within the previous 4 months).

Patients with preexisting coronary artery disease (CAD) and other CAD risk factors (e.g., hypertension, cigarette smoking) were not excluded. Patients taking thyroid hormone who had normal thyroxine levels and patients with diabetes who were treated by diet alone (fasting blood sugar ≤140 mg/dl) also were not excluded.

Experimental design and hypotheses: This multicenter trial was designed as a randomized, placebo-controlled, double-blind trial with 5 parallel treatment groups of approximately equal size. After a 4- to 6-week diet-only run-in baseline period, patients were treated for 48 weeks with both diet and 1 of the following 5 regimens: lovastatin, 20 or 40 mg with the evening meal (qpm), and 20 or 40 mg twice daily, or placebo. The use of placebo was justified by the lack of evidence to suggest that 48 weeks of therapy would significantly reduce the risk of CAD in patients under medical supervision who are encouraged to pursue an appropriate diet.[11,12] Adherence to the American Heart Association phase I diet or a more stringent diet was encouraged throughout the trial, and alert levels for unacceptable elevations in lipids were set. Each center obtained ethics committee approval of the study and written informed consent was obtained from participants. The trial was initiated before publication of the National Cholesterol Education Program (NCEP) consensus guidelines for the management of hypercholesterolemia in adults.[13]

The sponsor (Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania) was responsible for protocol development and policy decisions. Responsibility for execution of the study was contracted to Clinical Research International, Inc. (Research Triangle Park, North Carolina). SmithKline Bioscience Laboratories (Clinical Trials Division, Van Nuys, California) served as the central laboratory for the study.

A sample size of at least 1,418 patients per treatment group completing 48 weeks of therapy was required to allow for detection of a 0.1 vs 1.0% between-group difference in the incidence of 2 successive serum transaminase elevations >3 times the upper limit of normal with 90% power using a 5% α level 2-tailed test. This sample size would also allow for the detection of a difference of 3 percentage points (e.g., 5 vs 8%) in the proportion of patients achieving plasma total cholesterol levels <200 mg/dl and a difference of 5 percentage points (e.g., 25 vs 30%) in the incidence of lens findings by slit-lamp examination. The total number of patients to be randomized to drug therapy (n = 8,000) was based on the assumption that 12% would withdraw early.

Masking of treatment groups was achieved with the use of identical tablet images for active doses and placebo. The only difference in tablet composition was the relative amount of lovastatin (0 to 40 mg) and lactose (169 to 129 mg) used to equalize tablet weights. All patients received AM- and PM-labeled bottles to allow for twice-a-day dosing. Patients, investigators and study monitors were blinded to treatment group assignment. To maintain the blind, the central laboratory revealed lipid values during the study only when they were elevated beyond predefined alert levels (total cholesterol >350 mg/dl or triglycerides >800 mg/dl). In addition, the individual treatment assignments remained unknown to all those involved in patient monitoring, data collection, coding and baseline data analysis until patients had com-

TABLE I Schedule of Study Measurements by Visit Week

Measurement	Baseline (Diet Only)				Drug Therapy (Plus Diet)							
Visit Week	Screening −6	Qualifying −2		Allocation 0	6	12	18	24	30	36	42	48
Laboratory												
Lipids	x	x		x		x		x		x		x
Safety		x		x	x	x	x	x	x	x	x	x
Clinical												
Preexisting conditions				x								
Concomitant medication				x	x	x	x	x	x	x	x	x
Adverse experiences					x	x	x	x	x	x	x	x
Physical*			x									x
Ophthalmologic*			x					x				x
ECG*			x					x				x
Chest x-ray*			x									
Other												
Demographic				x								
Anthropometric				x	x	x	x	x	x	x	x	x
Health habits				x	x	x	x	x	x	x	x	x
Compliance				x	x	x	x	x	x	x	x	x

* Baseline examinations to be performed after qualifying but before allocation to drug therapy.
ECG = electrocardiogram.

pleted the study and all major data-related questions had been resolved.

The analysis of efficacy will address the following specific questions as they relate to total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, total cholesterol/HDL cholesterol ratio and LDL/HDL cholesterol ratio: (1) Does lovastatin 20 mg qpm differ from placebo in its effects on lipid levels? (2) Do higher total daily doses (20 vs 40 vs 80 mg) of lovastatin correspondingly increase the effect on lipid levels? (3) Does lovastatin 20 mg twice daily differ from lovastatin 40 mg qpm in its effects on lipid levels?

The safety analyses will also address dose-response relationships. Included in these analyses will be tests of the dose-response relations for 2 successive serum transaminase elevations exceeding 3 times the upper limit of normal (patient distributions by time) and the distribution of change in slit-lamp lenticular findings for each of 7 lens categories after 48 weeks of treatment.

Intervention periods: The study was divided into 2 periods: a baseline diet-only period lasting 4 to 6 weeks, and a diet and drug therapy period lasting 48 weeks. Table I summarizes scheduled protocol visits and tests.

The baseline period began with a screening visit at which time fasting plasma lipid levels and other inclusion/exclusion critera were determined. Patients who met the clinical (nonlipid) inclusion/exclusion criteria were instructed to initiate or maintain an American Heart Association phase I diet or a more stringent diet and progressed to a qualifying visit, which took place 2 to 4 weeks after the screening visit. The fasting plasma lipid levels at the qualifying visit were used to determine lipid eligibility for entry into the trial. Because of the analytic and inherent biologic variation in cholesterol measurement,[14] patients within 3% of the entrance criteria for total and LDL cholesterol were allowed to qualify for lipid eligibility if they had a prior history of measurements within the protocol range. Serum chemistry and hematology testing were performed as well as urinalysis, physical examination, electrocardiography, chest x-ray and ophthalmologic examination.

After 2 weeks, patients meeting the lipid and clinical criteria returned for the allocation visit and were randomized to drug therapy. Blood samples were drawn for determination of fasting plasma lipid levels, and serum chemistry and hematology testing was performed. Demographic information, family history, preexisting conditions and concomitant therapies were recorded. During the next 48 weeks, visits were scheduled every 6 weeks. Patient symptoms were recorded, and serum chemistry and hematology determinations were obtained at each visit. Fasting plasma lipid determinations were obtained every 12 weeks. No other formal interventions (e.g., smoking cessation, exercise) were required by the protocol.

Laboratory determinations: All protocol-specified determinations were performed by the central laboratory to ensure standardization of laboratory procedures. Blood samples were collected by venipuncture while the participants, who had fasted overnight, were seated. Plasma samples were prepared by collection with ethylenediaminetetraacetic acid (EDTA) and subsequently centrifuged. Serum specimens were prepared by allowing the specimen to clot for 30 to 60 minutes and subsequently centrifuging. A separate serum vial was prepared and frozen for CPK determination. Specimens for determination of complete blood count and differential and platelet counts were prepared by collection with EDTA. Specimens were picked up by special courier, maintained in refrigerated or frozen (sample for CPK determination only) conditions and delivered to the central laboratory.

Fasting plasma total cholesterol was analyzed with the use of a standard enzymatic technique to quantitate quinoneimine dye formation after hydrolysis and oxida-

TABLE II Predefined Alert Levels For Laboratory Measurements

Laboratory Determination	Reference Range (Age/Sex Specification)	Alert Level*	Immediate Alert Level†
SGOT (U/liter)	0–50 (<66) 0–65 (66+)	>100	>150
SGPT (U/liter)	0–55	>110	>165
CPK, total (U/liter)	0–235 (Male) 0–190 (Female)	>500	>1,000
Creatine (mg/dl)	0.7–1.4 (<66) 0.7–1.8 (66+)	None	>3.5
Bilirubin, total (mg/dl)	0.2–1.2 (<66) 0.2–1.4 (66+)	None	>4.0
Alkaline phosphatase (U/liter)	20–140	None	None
Fasting blood glucose (mg/dl)	70–115 (<51) 80–125 (51+)	>140	<50 or >500
Hemoglobin (g/dl)	13.8–17.2 (<66/male) 11.8–16.8 (66+/male) 12.0–15.6 (<66/female) 11.1–15.5 (66+/female)	None	<11.0 (male) <9.0 (female)
Hematocrit (%)	41–50 (<66/male) 36–49 (66+/male) 35–46 (<66/female) 33–46 (66+/female)	None	<33 (male) <27 (female)
White blood count (10^3/mm^3)	3.9–10.1 (<66) 3.8–10.8 (66+)	None	<2.0 or >20.0
Platelet count (/mm^3)	130.000–400,000	None	<50,000 or >800,000
Plasma total cholesterol (mg/dl)	NA	None	>350
Triglycerides (mg/dl)	NA	>350	>800

* Flagged by asterisk on laboratory reports to investigators.

† Immediate phone notification to investigator, contractor and sponsoring company except for lipid alert levels, which were not sent to investigator unless necessary for patient safety.

CPK = creatine phosphokinase; NA = not applicable; SGOT = aspartate aminotransferase; SGPT = alanine aminotransferase.

tion of cholesterol.[15] HDL cholesterol was analyzed after precipitation of very low density lipoprotein and LDL with phosphotungstic acid and magnesium chloride. HDL cholesterol was then measured by reaction with cholesterol esterase and cholesterol oxidase.[16] Triglycerides were determined after their conversion to free fatty acids and glycerol by measurement of the absorbance of the reaction of glycerol with glycerol kinase and pyruvate kinase at 340 nm.[17] LDL cholesterol levels were calculated with the use of the Friedewald equation.[18]

After the trial was initiated, part I testing of the central laboratory in the Centers for Disease Control (CDC) Lipid Standardization Program revealed a systematically fixed high bias for total cholesterol values (approximately 6% above CDC target mean). To correct the bias, recalibration and instrument (but not methodology) changes were suggested. Before making the changes, 2 sets of parallel tests (old vs new machine) were undertaken to confirm the bias and to ensure that a stable correction factor could be applied to samples analyzed before the instrument change. The 2 sets of patient samples (n_1 = 271, n_2 = 398) were collected and analyzed over separate 2-week intervals. The results confirmed the high bias for total cholesterol values, with linear regression coefficients (fitted without intercept) between the old instrument (y) and new instrument (x) of 0.954 and 0.945 and r^2 of 0.9997 and 0.9994 for the 2 sets of samples, respectively. Therefore, results for total cholesterol values before the instrument change were corrected by multiplying the result by 0.95. Triglyceride and HDL cholesterol values were unaffected by the instrument change. With the instrument change, the central laboratory was able to meet the CDC standardization criteria for total and HDL cholesterol. Of the 8,245 patients randomized, 6,747 (82%) had at least 1 baseline lipid determination measured before the instrument change.

Triglyceride determinations did not meet CDC standardization criteria. An artificially high mean bias resulted from failure of the procedure to correct for the free glycerol content of samples. The amount of bias was determined by split-sample assay comparing the values reported by the central laboratory with those reported by the CDC-standardized laboratory. Two sets of patient samples (n_1 = 75, n_2 = 75) showed that the mean was consistently overestimated by 19.2 mg/dl (12%), resulting in an expected 3.8 mg/dl (2%) mean underestimation of LDL cholesterol by the central laboratory. No correction factor was applied and, to date, internal reliability samples show no systematic drift in any of the mean lipid levels. This bias will have no effect on individual lipid responses for the efficacy analysis. The only likely effect was a small increase in the number of patients excluded from participation because of low LDL cholesterol levels.

The following serum assays were performed with the use of standard methodology at each scheduled visit after the screening visit: alanine aminotransferase (SGPT),

TABLE III Demographic Characteristics of Patients Allocated to Drug Therapy

		Treatment Group				
Characteristic	All Patients (n = 8,245)	Placebo (n = 1,663)	20 mg qpm (n = 1,642)	40 mg qpm (n = 1,645)	20 mg bid (n = 1,646)	40 mg bid (n = 1,649)
Age Group*						
% ≤44	14.8	14.1	15.2	15.3	13.6	16.1
% 45–49	10.1	10.1	10.8	9.2	9.7	10.9
% 50–54	13.6	14.1	13.1	13.7	13.4	13.8
% 55–59	19.2	18.4	20.3	19.8	19.2	18.2
% 60–64	21.9	21.5	21.2	21.9	23.0	21.8
% 65+	20.4	21.8	19.5	20.1	21.1	19.2
Sex						
% male	58.9	58.3	60.1	59.0	57.8	59.2
% female	41.1	41.7	39.9	41.0	42.2	40.8
Age* by sex (mean ± SD)						
Male	53.9 ± 10.4	54.1 ± 10.4	53.8 ± 10.1	53.5 ± 10.3	54.6 ± 10.3	53.5 ± 10.6
Female	58.4 ± 7.8	58.7 ± 7.6	58.3 ± 8.0	58.8 ± 7.8	58.5 ± 7.6	57.7 ± 8.2
Total	55.8 ± 9.7	56.0 ± 9.6	55.6 ± 9.6	55.7 ± 9.7	56.2 ± 9.5	55.2 ± 9.9
Race						
% White	91.7	91.5	91.4	92.6	91.4	91.3
% Black	5.6	5.5	5.8	5.0	5.5	6.0
% Hispanic	1.9	2.2	1.8	1.6	2.2	1.9
% Oriental	0.6	0.6	0.6	0.5	0.8	0.3
% Other	0.3	0.2	0.4	0.2	0.1	0.4
Years of school†						
% 1–6	1.1	1.1	0.9	1.7	0.9	1.1
% 7–12	40.0	39.3	40.5	39.5	41.1	39.7
% 13+	58.9	59.5	58.6	58.8	58.0	59.2

* At time of randomization.
† Excludes 17 patients with missing information.
SD = standard deviation.

aspartate aminotransferase (SGOT), CPK, total bilirubin, alkaline phosphatase, fasting blood glucose and creatinine.[19,20] Complete blood count included estimates of hemoglobin, hematocrit, white blood cells with a differential count, and platelets. In addition, urinalysis was performed for the detection of protein, sugar, leukocytes and erythrocytes if a screening urine dipstick showed the presence of protein, blood cells or nitrite.

Demographic characteristics and health profile: At the allocation visit, demographic characteristics including age, race, gender and years of school completed were recorded. At the same time, participants were questioned about a family history of cardiovascular disease (myocardial infarction, stroke, hypertension) or diabetes mellitus.

Beginning at allocation, height and weight, blood pressure (sitting) and temperature were recorded at each visit. Methods similar to those described by others[21] were used to question participants about their health habits including the current amount of cigarette smoking, the weekly amount of strenuous exercise or hard physical labor (none, <3 times, ≥3 times), and alcohol intake. Compliance with study diet was assessed by patient self-reporting of the amount of time the study diet was maintained during the previous 6 weeks (response categories were none of the time, less than half the time, half the time, most of the time, and all of the time). Concomitant medications, preexisting conditions and adverse experiences (defined as any deterioration in the health status of a patient, independent of cause, that occurred during the course of the trial) were recorded and subsequently coded. Systematic guidelines for coding allowed grouping of actual terms used to describe experiences or therapies into categories representing similar clinical conditions or drug classes.[22]

Ophthalmologic examination: A detailed ophthalmologic examination was performed at the allocation visit and at study weeks 24 and 48. Ophthalmologists were not to refer to prior examination findings when classifying the findings from the current examination. The findings from slit-lamp examination of the lens were recorded with the use of a system for classifying the presence and extent of findings in the cortex, nucleus and subcapsular regions of the lens.[23] Ophthalmologists were given written instructions along with photographic guidelines to increase the reliability of the classifications, and findings were recorded on standardized forms.

Safety monitoring: Procedures were developed to monitor safety for both individual patients and the entire patient cohort. The protocol required immediate phone contact with study monitors for any serious clinical adverse event experienced by a patient (death, any life-threatening experience, hospitalization, permanent or severe disability, overdose or cancer). Details regarding the suspected relation to drug therapy, patient disposition in the trial and further follow-up were discussed at the time of notification. The treatment code was broken only un-

TABLE IV Baseline Health Characteristics of Patients Allocated to Drug Therapy

Characteristics*	All Patients (n = 8,245)	Treatment Group (%) Placebo (n = 1,663)	20 mg qpm (n = 1,642)	40 mg qpm (n = 1,645)	20 mg bid (n = 1,646)	40 mg bid (n = 1,649)
Current cigarette smoking						
None	81.7	81.8	81.9	81.9	82.4	82.3
1–10/day	7.7	6.9	8.1	8.1	8.4	7.3
>10/day	10.6	11.3	12.2	10.0	9.2	10.4
Overweight						
≥30%†	17.3	16.8	18.2	17.1	16.7	17.7
Alcohol consumption						
None	44.3	44.0	45.3	44.5	43.5	44.1
1–7 drinks/wk	42.0	42.5	41.0	42.4	42.2	42.0
>7 drinks/wk	13.7	13.5	13.6	13.1	14.2	13.9
Exercise category (strenuous/wk)						
None	67.0	67.3	67.2	66.4	67.8	66.0
<3 times	7.4	7.3	7.7	6.7	7.9	7.5
≥3 times	25.6	25.4	25.1	26.8	24.3	26.5
Dietary compliance						
None	0.4	0.5	0.4	0.7	0.1	0.5
<1/2	3.1	2.6	3.6	3.0	3.2	2.9
1/2	13.9	14.1	12.7	13.7	14.8	14.0
Most	65.6	66.1	66.0	66.3	65.0	64.7
All	17.0	16.7	17.2	16.3	16.8	17.8

* Excludes the following number of patients with missing characteristic information: smoking (n = 1), overweight (n = 16), alcohol (n = 1), exercise (n = 1), diet (n = 1).
† Based on sex-specific body mass index (male ≥ 29.5 kg/m²; female ≥ 29.1 kg/m²).

der the following conditions: (1) a need to manage a medical emergency (after consultation with a study monitor), and (2) the occurrence of a serious event considered to be drug-related and not previously described in the investigator's confidential brochure or the lovastatin package circular. In addition to the notification system described, case report forms were reviewed to detect previously unreported serious events. The decision to withdraw a patient from the trial as a result of clinical adverse experiences was made by the investigator.

Results of laboratory tests were monitored centrally on a daily basis. Test results falling into an alert level (Table II) prompted contact with the investigator to discuss appropriate retests and disposition of the patient. Based on prior experience with lovastatin, formal criteria for retesting and trial discontinuation were developed for liver transaminase and CPK elevations. Treatment codes were not broken in these instances. Patients who had liver transaminase elevations >3 times the upper limit of normal on 2 occasions within 1 week were to be withdrawn from the trial. Patients who maintained transaminase elevations between 2 and 3 times the upper limit of normal over a 12-week period (retested every 3 weeks) were also to be withdrawn. Patients who developed CPK levels >1,000 U/liter were to be retested within 1 week. The decision to withdraw patients with successive CPK elevations was left to the clinical judgment of the investigator.

Serious adverse experiences and alert level liver transaminase and CPK elevations were cumulated and reported monthly (blinded to treatment except as previously noted) to an independent monitoring committee of physicians and statisticians. The committee reviewed the blinded aggregate experience to determine if there were events that appeared to occur with unexpected frequency. When necessary, relative comparisons to published information were made. To assist the committee in determining rates of events, person-time exposure rates were calculated based on the cumulative number of patients with specimens submitted to the central laboratory.

Baseline definitions: Patients who were all at a high-risk level of LDL cholesterol were classified into 2 groups, retrospectively, using NCEP criteria[13]: those with CAD or 2 or more CAD risk factors vs those with no CAD and fewer than 2 CAD risk factors. The classification was based on a history of CAD or meeting 2 or more of the following criteria: male gender, parent/sibling with myocardial infarction before age 55, current cigarette smoking (>10 per day), hypertension, HDL <35 mg/dl at 2 consecutive baseline visits, severe obesity (defined as ≥30% overweight using 1983 Metropolitan tables)[24] or history of stroke, peripheral vascular disease or diabetes mellitus. Preexisting CAD was classified into prior myocardial infarction, angina and other categories (e.g., coronary atherosclerosis, postcoronary artery bypass graft or angioplasty).

Unless otherwise noted, baseline lipid and safety laboratory levels for a patient were defined as the average of 2 determinations obtained closest in time to the day of randomization. When lipid and glucose determinations were obtained, patients were required to be fasting. In the absence of 2 fasting determinations (which occurred <10% of the time), a single fasting value was defined as the baseline level. If both determinations were nonfasting (which occurred <0.1% of the time), then the one made closest to the day of randomization was defined as the baseline level. Other baseline laboratory levels were de-

TABLE V Cardiovascular Disease History and Selected Medication Taken Within 30 Days of Allocation to Drug Therapy

Characteristic	All Patients (n = 8,245)	Treatment Group (%) Placebo (n = 1,663)	20 mg qpm (n = 1,642)	40 mg qpm (n = 1,645)	20 mg bid (n = 1,646)	40 mg bid (n = 1,649)
Cardiovascular and associated disease history	57.2	58.0	58.2	56.5	57.5	55.9
Hypertension	39.6	40.7	40.8	38.3	40.2	38.0
CAD	28.7	29.3	29.7	27.7	28.6	28.1
Stroke	3.9	5.0	3.8	3.8	3.2	3.8
Peripheral vascular disease	2.5	2.9	2.3	2.7	2.2	2.4
Diabetes	1.1	1.1	1.0	1.2	1.1	1.3
NCEP* classification						
CAD or 2 or more CAD risk factors	61.8	61.3	63.6	62.5	61.3	60.4
Antihypertensive/antianginal medication						
β blockers	20.8	22.9	21.3	20.8	21.3	17.5
Calcium antagonists	15.1	15.3	15.4	14.8	14.2	15.9
Diuretics	12.5	13.1	12.6	12.0	12.5	12.2
ACE inhibitors	7.0	6.6	6.3	7.6	7.2	7.6
Centrally acting agents	2.3	2.0	2.4	2.3	2.8	2.2
α blockers	1.0	1.1	0.8	0.9	1.0	1.0

* NCEP criteria (discussed in text). NCEP = National Cholesterol Education Program.
ACE = angiotensin-converting enzyme inhibitors; CAD = coronary artery disease.

termined in a similar fashion without the fasting requirement. Because of mishandled specimens and other technical problems, the allocation visit laboratory determinations for a small portion of patients (<5%) were obtained after the day of randomization; these were not included as baseline data.

FINDINGS AT BASELINE

The trial was initiated in April 1987. In all, 362 primary investigators were selected for participation from 42 states in the continental United States and the District of Columbia. From May 1987 to June 1988, 17,125 patients were screened for participation in the trial. Of these, 13,718 advanced to a qualifying visit, and 8,245 were randomized to therapy: 1,642 to lovastatin 20 mg qpm, 1,645 to 40 mg qpm, 1,646 to 20 mg bid, 1,649 to 40 mg bid and 1,663 to placebo.

Effectiveness of randomization procedure: Mean values were calculated by treatment group for key baseline variables. Inspection of the data revealed a near equivalence among treatment groups with regard to demographic characteristics, cardiovascular disease history, concurrent use of selected antihypertensive/antianginal medications, and mean plasma lipid/lipoprotein and safety laboratory values.

Demographic characteristics (Table III): Of the 8,245 patients randomized to drug therapy, 59% were men and 41% were women. The mean age of participants was 56 years; men were, on average, 4.5 years younger (53.9 years) than women (58.4 years). The majority of patients were white (92%), and 59% had completed at least 1 year of education beyond high school.

Health habits (Table IV): Current cigarette smoking was reported by 18% of patients, and 17% were ≥30% overweight based on body mass index. Alcohol consumption was reported at a level of up to 1 drink per day by 42% of patients and more than 1 drink per day by 14%; abstinence was reported by 44%. Strenuous exercise was reported at a frequency of <3 times per week by 7% of patients, ≥3 times per week by 26% and none weekly by

TABLE VI Baseline Fasting Plasma Lipid and Lipoprotein Levels (mg/dl) of Patients Allocated to Drug Therapy

Lipid/Lipoprotein	All Patients	Treatment Group Placebo	20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
Total cholesterol	258.1 ± 20.5	257.4 ± 20.3	257.9 ± 20.5	258.5 ± 20.0	258.7 ± 20.7	258.1 ± 21.0
LDL cholesterol	180.0 ± 20.7*	179.4 ± 20.4*	180.2 ± 20.6	180.0 ± 20.6	180.6 ± 20.5	179.7 ± 21.2
HDL cholesterol	45.0 ± 12.1	44.8 ± 12.0	45.0 ± 12.4	45.2 ± 11.8	45.0 ± 11.9	45.2 ± 12.6
(% < 35 mg/dl)	(14.1%)	(14.2%)	(15.0%)	(12.3%)	(14.1%)	(15.1%)
Triglycerides						
Median	155	156	152	156	157	154
25th percentile	115	117	113	115	116	116
75th percentile	208	210	204	211	205	210

* Excludes 1 patient with missing LDL cholesterol value at baseline.
All values for total, LDL and HDL cholesterol are expressed as mean ± standard deviation.
LDL = low-density lipoprotein; HDL = high-density lipoprotein.

TABLE VII Baseline Safety Laboratory Data of Patients Allocated to Drug Theapy

Laboratory Measurement*	All Patients	Treatment Group Placebo	20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
SGOT (U/liter)	20.0 ± 7.8	19.8 ± 6.4	19.9 ± 6.0	19.9 ± 6.1	19.9 ± 6.2	20.4 ± 12.3
SGPT (U/liter)	24.5 ± 12.0	24.3 ± 12.1	24.4 ± 11.3	24.4 ± 10.8	24.3 ± 11.5	25.1 ± 14.0
CPK (U/liter)	125.4 ± 87.2	126.5 ± 89.9	127.3 ± 94.1	120.6 ± 71.6	125.9 ± 86.4	126.5 ± 91.9
Creatinine (mg/dl)	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
Total bilirubin (mg/dl)	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2
Alkaline phosphatase (U/liter)	87.0 ± 25.0	86.9 ± 24.6	86.9 ± 25.4	87.1 ± 28.4	86.6 ± 22.5	87.5 ± 23.9
Fasting glucose (mg/dl)	101.9 ± 11.8	102.2 ± 12.1	102.1 ± 11.6	101.8 ± 12.0	101.8 ± 12.1	101.4 ± 11.2
Hemoglobin (g/dl)	15.0 ± 1.3	15.0 ± 1.3	15.0 ± 1.3	15.0 ± 1.3	15.1 ± 1.3	15.1 ± 1.3
WBC (10^3/mm^3)	6.3 ± 1.7	6.3 ± 1.7	6.4 ± 1.7	6.3 ± 1.7	6.2 ± 1.6	6.3 ± 1.7
Platelet count (10^9/liter)	240.6 ± 54.4	238.4 ± 54.6	242.2 ± 54.6	240.8 ± 54.1	239.8 ± 54.2	241.8 ± 54.6

* Excludes the following number of patients with missing baseline safety laboratory measurements: platelet count (n = 34); CPK (n = 23); hemoglobin, WBC (n = 14); alkaline phosphatase (n = 5); SGOT, SGPT, creatinine, bilirubin, fasting glucose (n = 4).
All values are expressed as mean ± standard deviation.
WBC = white blood cell; other abbreviations as in Tables II and III.

67%. About 83% of patients in each treatment group reported compliance with the study diet "most" or "all" of the time during the baseline period.

Cardiovascular history (Table V): Overall, 62% of patients had CAD or 2 or more CAD risk factors by NCEP criteria in addition to the high-risk level of LDL cholesterol. Preexisting cardiovascular or associated disease (stroke, peripheral vascular disease or diabetes) was reported by 57% of patients, with hypertension (40%) and CAD (29%) being the most prevalent conditions. Because there was a high prevalence of hypertension and CAD, a substantial portion of patients were taking antihypertensive and antianginal medication; β-blocking agents (21%), calcium antagonists (15%) and diuretics (13%) were the most prevalent. Among women, 24% reported taking estrogens and 7% reported taking progestins.

Lipid/lipoprotein levels at baseline: The baseline mean lipid/lipoprotein levels were equivalent among treatment groups (Table VI). For the total cohort, baseline mean values for total cholesterol, LDL cholesterol and HDL cholesterol were approximately 258, 180 and 45 mg/dl, respectively. The median triglyceride level was 155 mg/dl.

Only minor changes in lipid levels were observed during the 3 baseline visits. Mean total and LDL cholesterol levels each decreased by approximately 1 to 2% between screening and allocation (261.5 vs 258.0 mg/dl and 182.7 vs 179.2 mg/dl, respectively). The percentage of patients with a 20% change in fasting LDL cholesterol values between screening and allocation visits was 14%, with approximately equal numbers of patients showing an increase and a decrease. Mean HDL cholesterol levels decreased slightly from screening to allocation (45.9 vs 45.1 mg/dl), whereas median triglycerides increased slightly (151 vs 155 mg/dl).

Laboratory safety data at baseline: Baseline mean laboratory safety data were nearly equivalent among treatment groups and well within the normal range (Table VII). For the total cohort, CPK was the most frequently elevated baseline value. Nearly 9% of patients had an average baseline CPK above the normal range, and 101 patients (1%) had CPK values >500 U/liter at either the qualifying or allocation visits. The percentages of patients with elevations in other baseline safety laboratory values were: hemoglobin (7%), fasting blood glucose (5%), serum creatinine (4%), white blood cells (3%), SGOT (0.2%), SGPT (2.0%), alkaline phosphatase (2.7%) and bilirubin (0.7%). The percentage of patients with baseline safety values below the normal range were: hemoglobin (2%), white blood cells (2%) and platelet count (0.7%).

Correlates of low high-density lipoprotein cholesterol: As HDL was the only lipid/lipoprotein unrestricted by study entrance criteria, its relation to other CAD risk factors was examined (Table VIII). Mean levels of HDL cholesterol were approximately 10 mg/dl higher in women than in men, with no consistent difference in levels with age. For both men and women, the prevalence of low HDL cholesterol levels was found to be higher in white patients, those reporting no strenuous exercise, those reporting abstinence from alcohol, cigarette smokers, the obese and those with a personal or family history of myocardial infarction before age 55.

DISCUSSION

The design and implementation of this study are noteworthy in several respects and should allow a more definitive ascertainment of the efficacy of lovastatin in its primary role as a potent LDL cholesterol-reducing drug and further evaluation of safety issues concerning its use in typical clinical applications. Significant features of the study design were its use of placebo-control, double-blinding and the minimization of other confounding factors. Design calculations based on the study objectives indicated that a minimal sample size of 1,418 participants completing the study was required for each treatment (total of 7,090 in 5 groups). Recruitment yielded a total of 8,245 randomized participants, exceeding the minimal goal by more than 16% and compensating for an expected 12% dropout rate.

The equivalence of treatment groups at baseline will allow valid between-group comparisons for the variables being monitored. The enrollment into the study of approximately 48% of those initially screened reflects in part the effort to minimize exclusion criteria other than lipid/lipoprotein-related parameters, thereby permitting

TABLE VIII Frequency of Low High-Density Lipoprotein Cholesterol* by Selected Patient Characteristics at Baseline

	Male HDL-C Level (mg/dl)			Female HDL-C Level (mg/dl)		
Characteristic	No. of Pts.	% <35	% ≥35	No. of Pts.	% <35	% ≥35
Race						
White	4,512	22	78	3,045	4	96
Black	215	12	88	244	2	98
Other	128	21	79	101	5	95
Exercise level						
None	2,922	24	76	2,598	4	96
<3 times/week	437	20	80	174	2	98
≥ 3 times/week	1,495	17	83	618	4	96
Alcohol consumption						
None	1,723	30	70	1,929	5	95
1–7 drinks/week	2,186	19	81	1,279	4	96
>7 drinks/week	945	10	90	182	1	99
Cigarette smoking						
None	3,965	18	82	2,770	3	97
1–10/day	364	26	74	269	6	94
>10 day	525	38	62	351	10	90
Overweight						
No	4,093	20	80	2,712	4	96
Yes	748	27	73	676	5	95
Prior myocardial infarction						
No	3,612	18	82	3,098	4	96
Yes; ≥ age 55	417	26	74	164	9	91
Yes; < age 55	781	31	69	108	10	90
Yes; age unknown	6	33	77	3	33	77
Family history of myocardial infarction						
No	2,228	19	81	1,378	4	96
Yes; ≥ age 55	1,333	21	79	1,040	4	96
Yes; < age 55	979	26	74	763	5	95
Yes; age unknown	55	29	71	42	0	100

* Low HDL cholesterol defined as <35 mg/dl at any baseline visit.
HDL-C = high-density lipoprotein cholesterol.

maximal generalizability of the findings. The lipid criteria for study entrance (240 to 300 mg/dl for total cholesterol, ≥160 mg/dl for LDL cholesterol) are representative of the levels of a majority of patients currently recommended for drug therapy by the NCEP.[13] The study also includes those with preexisting CAD (29%), those classified by NCEP criteria as having CAD or 2 or more CAD risk factors (62%) in addition to a high-risk level of LDL cholesterol, and the largest number of hypercholesterolemic hypertensive patients (n = 3,264) ever studied. The generalizability of the findings should also be enhanced by the inclusion of a large number (362) of participating centers throughout the United States.

The tendency to some selection bias in study populations is typically observed in clinical trials and related studies, and in part reflects the characteristics of subjects with interest and willingness to volunteer for participation. Comparison of the demographic characteristics of the study cohort (Tables III, IV) with the United States population reveals an over-representation of whites (92 vs 86%, respectively) and an under-representation of minorities (6 vs 12%, respectively).[25] In addition, the study population, compared with the United States population, included a higher percentage of persons with education beyond the high school level (59 vs 36%, respectively) and lower percentages of current cigarette smokers (18 vs 35%) and persons who consume alcohol (56 vs 70%).[25]

Associations found between HDL cholesterol and patient demographic characteristics were similar to those reported by others.[26–28] For example, associations with HDL cholesterol observed in the Second National Health and Nutrition Examination Survey[27] that were also observed in this study population include higher mean HDL cholesterol levels in women and blacks, lower mean HDL cholesterol levels in obese patients, a direct relation between cigarette smoking and the prevalence of low HDL cholesterol, and an inverse relation between exercise levels and alcohol consumption and the prevalence of low HDL cholesterol. In addition, there was little variation in HDL cholesterol with age.

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SEPTEMBER 25, 1990

A Symposium: Primary and Secondary Prevention of Cardiovascular Disease

GUEST EDITORS:
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Professor of Medicine
Weiler Hospital of the Albert Einstein College of Medicine
Bronx, New York

Stanley H. Taylor, MD, PhD
Professor of Cardiology
University Department of Medical Cardiology
The General Infirmary
Leeds, United Kingdom

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The American Journal of Cardiology

SEPTEMBER 25, 1990 VOL. 66 NO. 9

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Introduction

William H. Frishman, MD, and Stanley H. Taylor, PhD, MD

Beta-adrenergic blocking drugs have been proved safe and effective for the treatment of patients with various cardiovascular disorders, which include systemic hypertension, angina pectoris and arrhythmia. Additionally, since 1965, β-blocking drugs have been considered possible therapy for extending the lives of patients who survive myocardial infarction (MI). On the basis of long-term clinical studies, the efficacy of β blockers in reducing the risk of mortality and nonfatal reinfarction in survivors of an acute MI has been conclusively shown. More controversial has been the role of β blockers that have partial agonist activity and their relative efficacy compared with drugs that lack this activity. The safety and effectiveness of β blockers in the subgroup of infarct survivors who are at a higher risk of subsequent mortality remain to be determined.

An international satellite symposium was held in March 1990, just prior to the Annual Scientific Sessions of the American College of Cardiology, to discuss the most recent trials assessing the protective actions of β blockers in patients with hypertension and in patients who survived an acute MI. The written reports of the participants, contained in this supplement, highlight the symposium proceedings.

Hampton reviews the results of 25 years of clinical trials that were designed to assess the efficacy and safety of various β blockers and calcium antagonists in prolonging the life of survivors of acute MI. The results, to date, demonstrate an overall advantage for β blockers.

Singh also reviews the clinical trial experiences with β blockers, calcium antagonists and antiarrhythmic drugs for prolonging life in patients who survived MI. The effects of some class I antiarrhythmic drugs show potential for harm when administered to these patients. Preliminary data suggest that class III antiarrhythmic agents, especially amiodarone, may have similar advantages to β blockers in reducing mortality among survivors of MI.

Jaillon discusses the theoretical advantages of using β blockers with partial agonist effects in patients with systemic hypertension. Partial agonist β blockers can produce arterial vasodilation and increase arterial compliance. Jaillon also discusses the potential use of β blockers with moderate partial agonist activity for decreasing the postinfarction mortality rate.

Acebutolol, a long-acting β blocker having both β_1-selectivity and moderate partial agonist effects, was studied in a recent multicenter, placebo-controlled trial, Acebutolol et Prévention Secondaire de l'Infarctus (APSI). The APSI trial, conducted in France, was specifically carried out to evaluate the effects of acebutolol compared with those of placebo in high-risk survivors of acute MI. Boissel presents the results of the APSI trial for the investigators. Compared with placebo, acebutolol reduced total mortality 48% and cardiovascular mortality 58% after 318 days. The results of the study resolve the controversy concerning the safety and efficacy of using a β blocker with moderate partial agonist activity as prophylactic therapy after MI in high-risk patients.

In the next article, Mascioli and colleagues describe the preliminary findings of the Treatment of Mild Hypertension Study (TOHMS), which was designed to compare the effects of nonpharmacologic therapy alone with those of each of 5 active drug regimens or placebo when combined with nonpharmacologic therapy. The study drugs included a β blocker (acebutolol), a calcium antagonist (amlodipine), a diuretic (chlorthalidone), an α_1 blocker (doxazosin) and an angiotensin-converting enzyme inhibitor (enalapril). Study end points include blood pressure reduction, drug tolerance and side effects, as well as effects on ventricular ectopy and left ventricular mass.

The next 4 articles discuss specific issues relevant to the treatment of hypertension. Kaplan describes the concept of arterial protection in assessing antihypertensive therapy: reducing blood pressure with drugs should prevent or reverse smooth muscle hypertrophy of arteriolar resistance vessels and atherosclerosis, primarily involving the larger arteries. However, there may be real differences among the various antihypertensive drugs in their ability to provide arterial protection. Levenson et al specifically address the issue of large vessel arterial damage with hypertension. They demonstrate that some antihypertensive drugs do not improve arterial compliance or distensibility while lowering blood pressure. The authors point to arterial compliance and wall shear stress as 2 main therapeutic targets in the physiopharmacologic approach to the effects of hypertension on atherogenesis. Weber provides information on automated ambulatory blood pressure monitoring, demonstrating how the monitoring technique has been used to measure the efficacy and duration of action of different antihypertensive drugs. He also emphasizes the need for antihypertensive therapy to provide 24-hour blood pressure control. In the final article, Schnaper addresses the issue of lipid and lipoprotein changes with antihypertensive drugs, with special attention given to the lipid-lowering effects of acebutolol.

Great advances have taken place in our ability to treat cardiovascular diseases. Various drug therapies not only prolong life but also improve its quality. However, additional research of the high quality of the reports presented at this symposium is needed.

The editors of this symposium are happy to share these highlights with the journal's readership.

Secondary Prevention of Acute Myocardial Infarction with Beta-Blocking Agents and Calcium Antagonists

John R. Hampton, DM, DPhil, FRCP

The discovery that β blockers possess clinically useful hypotensive, antianginal and antiarrhythmic properties has attracted the interest of clinicians, researchers and the pharmaceutical community alike. In addition, minor differences in a variety of ancillary properties have led to speculation that specific classes of drugs might have advantages over other classes. The enthusiasm that greeted reports from the first small trials, which showed that β blockers reduced the postmyocardial infarction mortality rate, attracted the commercial support necessary to evaluate different β blockers in this clinical setting. The plethora of β blockers that subsequently became available for study led to considerable improvement in both the design and implementation of large clinical trials. Despite apparent discrepancies in the results of various trials, meta-analysis indicates that most, if not all, β blockers reduce postinfarction mortality. However, because meta-analysis cannot recommend a particular drug or specific dose for use in an individual patient, clinical practice must be based on the results of individual trials, not on the conclusions of meta-analysis. The clinical utility of β blockers in the secondary prevention of myocardial infarction, coupled with experimental evidence that calcium antagonists reduce infarct size, led to a series of large studies designed to establish whether calcium antagonists have any effect on reducing mortality in patients with myocardial infarction. Lessons learned from the β-blocker trials permitted a more rapid evaluation of the efficacy of calcium antagonists in this setting. It is clear that, unlike β blockers, calcium antagonists are not effective in the secondary prevention of myocardial infarction.

(Am J Cardiol 1990;66:3C–8C)

Twenty-five years ago, Snow[1] reported that treatment with the β blocker propranolol reduced the mortality rate in patients with acute myocardial infarction. Since then, a plethora of β blockers has appeared on the market, and many trials of different drugs of this type have been conducted to confirm Snow's observations. Perhaps because of commercial pressures, β blockers have become the most extensively investigated of all drugs, with more patients being included in trials of β blockers than any other type of clinical trial.

One clear benefit of the trials of secondary prevention with β blockers has been considerable improvement in the design and analysis of clinical trials. Snow's trial, e.g., was far too small to show a statistically significant benefit from active treatment, and results of subsequent small trials were published before the importance of large studies became generally recognized. However, the small studies contributed to an increased awareness of different methods of trial analysis. Figure 1 depicts a typical example of an atenolol trial[2] that now is clearly seen to be much too small, but the style of data presentation that was developed to present the results of such studies[3] demonstrates 2 important general points. First, it is desirable to know the size and demographic characteristics of the population from which the trial patients were selected. Without this information, the results of a trial may well be "true," but they may not be applicable to the types of patients seen by clinicians in daily practice. Second, Figure 1 shows the importance of separating the "intention to treat" and the "explicative" or "on treatment" analyses. "Intention to treat" analysis includes all the patients randomized in the trial, whether or not they continued to take the medication to which they were randomized. In the trial shown in Figure 1, the reduction in total mortality associated with active treatment was not statistically significant (9% compared with 12% in the placebo group). Among those patients who continued with their allocated treatment, the effect of atenolol was more marked (3% mortality rate with atenolol vs 11% with placebo). Thus, "explicative" analysis suggests that the drug may have a beneficial effect. However, Figure 1 also shows that treatment with a β blocker may be harmful: the mortality rate was essentially the same among patients who continued or were withdrawn from placebo therapy (11 and 12%, respectively), but among those withdrawn from atenolol, the mortality rate was 18%. One possible explanation for these results is that β-blocking treatment selects those with low and high mortality rates; perhaps patients with severe cardiac disease who have a high mortality rate are unable to tolerate therapy with a β blocker.

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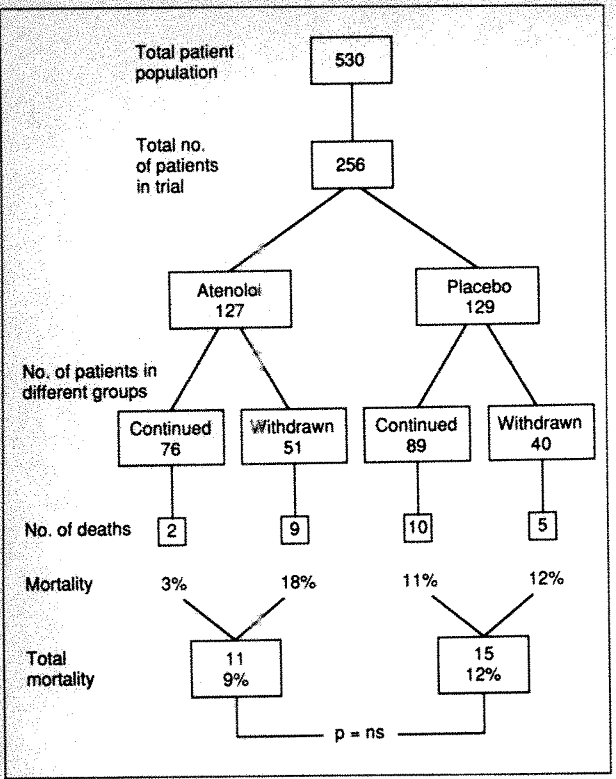


FIGURE 1. Results of a trial[2] comparing atenolol 100 mg daily with placebo in patients with acute myocardial infarction. Treatment was started immediately (66% within 8 hours).

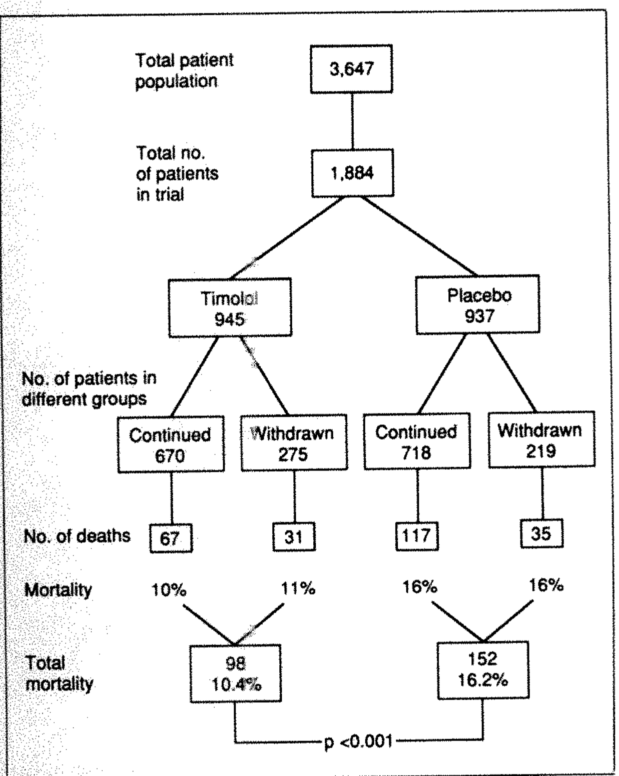


FIGURE 2. Results of the Norwegian Multicenter Postinfarction Trial of timolol.[4] Timolol was administered at a dosage of 10 mg twice daily from 7 to 28 days. Patients were followed for a mean duration of 17 months. The age range was 20 to 75 years.

BETA BLOCKERS AND SECONDARY PREVENTION

The first β-blocker postinfarction trial that provided all the necessary data to permit different analyses and was also large enough to demonstrate significant results was the Norwegian Multicenter Study on Timolol after Myocardial Infarction,[4] involving 1,884 patients (Fig. 2). This was a classic trial of considerable historical and clinical importance, which clearly demonstrated that therapy with a β blocker reduces postinfarction mortality. This study was followed by the Beta Blocker Heart Attack Trial (BHAT) of propranolol (Fig. 3).[5] The results of this study, which included a cohort of 3,837 postinfarction patients, were somewhat less satisfactory in that the outcome of patients withdrawn from treatment was not given. Nevertheless, BHAT demonstrated that a β blocker other than timolol was effective in secondary prevention, suggesting that reduction in mortality might be a class effect rather than a benefit limited to 1 drug. Furthermore, the patients admitted to the Norwegian and BHAT studies were clearly different, since the mortality rates in the placebo groups were 16.2 and 9.8%, respectively, suggesting that the benefit of β-blocking therapy applies to a wide variety of patients.

Detailed analysis of results was not routine in the early days of postinfarction trials, although this type of analysis is now common. It is difficult to describe the results of many trials in such detail; thus, the concept of "relative risk reduction" became widely accepted. As an example, if the mortality rate in the placebo group of a trial was

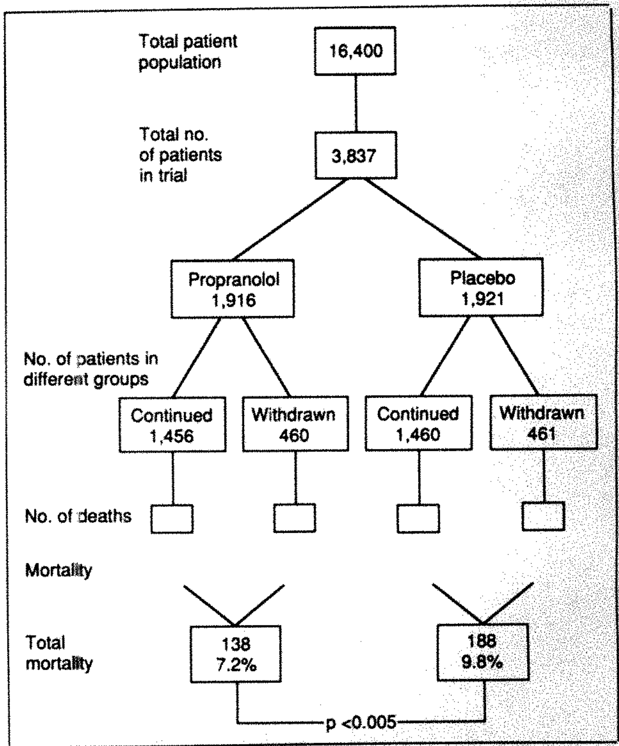


FIGURE 3. Results of the β-Blocker Heart Attack Trial (BHAT) of propranolol.[5] Propranolol was administered at a dosage of 120 to 240 mg/day. Age range was 30 to 69 years. Treatment was begun 14 days after myocardial infarction.

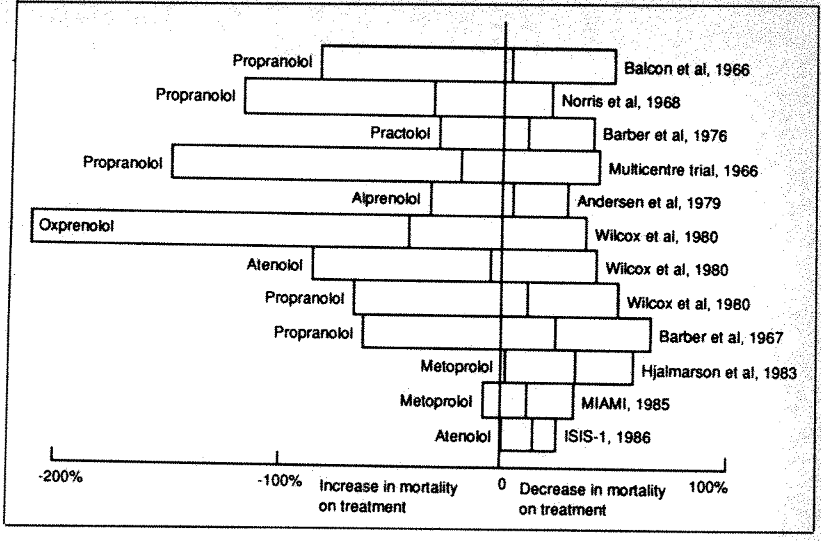


FIGURE 4. Beta blockers after myocardial infarction: 95% confidence intervals around the point estimates of relative risk reduction (or increase) associated with β-blocking treatment in early entry trials (treatment commenced within 72 hours of the onset of symptoms).

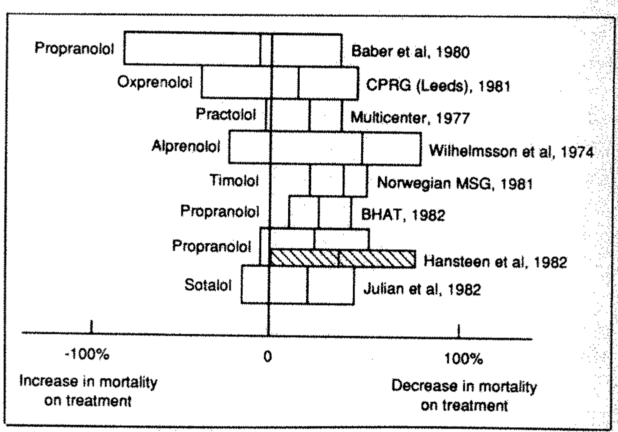


FIGURE 5. Beta blockers after myocardial infarction: 95% confidence intervals around the point estimates of relative risk reduction (or increase) associated with β-blocking treatment in late entry trials (treatment commenced >72 hours after the onset of symptoms).

50% and in the treated group 40%, the absolute risk reduction would be 10%, but the relative reduction (10 of 50%) would be 20%. It is, of course, essential to realize that a relative risk reduction of 20% also applies to a trial in which the event rate in the placebo group is 5% and that in the treatment group, 4%. Trial results are best expressed as the degree of confidence around the point estimate (i.e., the actual result) of relative risk reduction. This is usually expressed as the 95% confidence interval, which is the range within which one can be 95% certain that the "real" result must lie. Narrow confidence intervals depend on large numbers of patients and a higher placebo event rate; wide confidence intervals occur with small trials and a low event rate. A trial result is statistically significant only when the 95% confidence interval does not include zero effect.

Figures 4 and 5 show the 95% confidence intervals around the point estimates of the trials in which β-blocking treatment was begun early or late, respectively. Early treatment is defined arbitrarily as initiation of therapy within 72 hours of onset of symptoms. Late treatment is defined as initiation of therapy more than 72 hours after symptoms. The trials are arranged in sequence by publication date, and the individual references are given in the review by Yusuf et al.[6] Among the early entry trials, it can be seen that the metoprolol trial by Hjalmarson et al[7] demonstrated a significant result favoring active treatment, although the large Metoprolol in Acute Myocardial Infarction trial[8] (MIAMI) did not. The very large First International Study of Infarct Survival[9] (ISIS-1) also demonstrated a significantly positive result. Among the late-entry trials (Fig. 5), only the Norwegian timolol,[4] the Norwegian propranolol[10] and BHAT propranolol[5] studies showed a significant benefit resulting from β-blocking treatment; however, the pattern of results in the late entry trials seems to favor active treatment more than it does in the early entry trials.

Separation of the trials into "early" and "late" entry is useful clinically; early patients are unstable in their cardiac rhythms and hemodynamic parameters, but myocardial infarction cannot be diagnosed with certainty in the first few hours after admission. Late patients are stable, and only those with an established diagnosis need be included. The 2 groups of patients might well respond differently to β blockers, and it has to be accepted that the mode of action of these drugs in secondary prevention is not clear and could be different as the illness progresses.

Figures 4 and 5 show that β blockers have a more consistent effect in the late trials. When formal statistical techniques of meta-analysis are applied, the drugs appear to be equally efficacious in both early and late settings. However, ISIS-1, because of its large size, provides the most compelling evidence for early treatment.

Figures 4 and 5 clearly show that the ancillary properties of different β blockers cannot be considered clinically significant. Both selective (e.g., atenolol and metoprolol) and nonselective (e.g., propranolol) agents have been shown to reduce mortality. Intrinsic sympathomimetic activity has been associated with both a beneficial effect on mortality (practolol) and an actual increase in mortality (oxprenolol), and class III antiarrhythmic activity (sotalol) does not appear to confer any particular advantage in terms of preventing mortality. The only conclu-

TABLE I Calcium Antagonists After Myocardial Infarction

	Mortality (%)	
	Placebo	Active
Nifedipine		
Trent Study 1986[12]	6.3	6.7
SPRINT 1988[13]	5.7	5.8
Verapamil		
Danish 1984[14]	13.9	12.9
Diltiazem		
Non-Q-wave 1986[15]	3.1	3.8
MDPIT 1988[16]	13.5	13.5

MDPIT = Multicenter Diltiazem Postinfarction Trial; SPRINT = Secondary Prevention Reinfarction Israeli Nifedipine Trial.

sion from meta-analysis of the many trials of secondary prevention is that β blockers reduce mortality, an effect probably common to all drugs of this class.

CALCIUM ANTAGONISTS AND SECONDARY PREVENTION

The utility of the β blockers in reducing mortality, coupled with experimental evidence that calcium antagonists limit the size of infarct,[11] led to a series of large trials to establish whether calcium antagonists have any effect on reducing mortality in patients with myocardial infarction. Experience gained from the β-blocker trials permitted a more rapid evaluation of the efficacy of calcium antagonists. Unlike the β blockers, calcium antagonists were not shown to reduce mortality. Table I lists 5 large trials that were carried out with nifedipine (both early[12] and late[13] administration), verapamil[14] and diltiazem.[15,16] The results of these trials demonstrate approximately equal mortality rates in patients receiving placebo and active treatment (Table I).

The Multicenter Diltiazem Postinfarction Trial[16] enrolled 2,466 patients, of whom approximately 70% had had a Q-wave infarction. In patients with non-Q-wave infarction, diltiazem was reported to reduce reinfarction, but not death.[15] However, the significance of this result is uncertain because some of the definitions used in the study were inexact, and the observation has not been confirmed by subset analysis of the other trials. In conclusion, analysis of the secondary prevention trials with calcium antagonists shows that there is no preventive role for these drugs, although they can be useful in the treatment of angina pectoris.

SECONDARY PREVENTION BASED ON THE RESULTS OF CLINICAL TRIALS

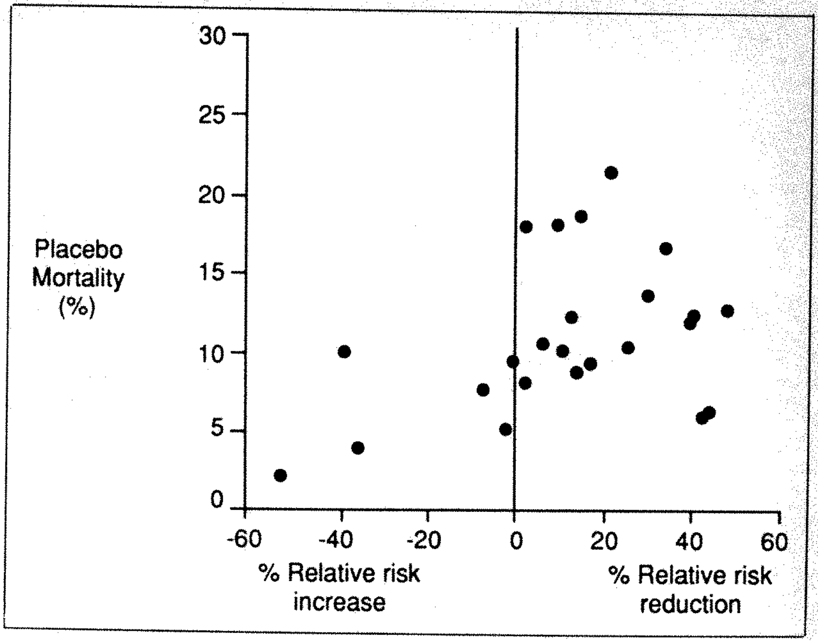
Meta-analysis of these trials of secondary prevention does not provide answers to several therapeutic questions of paramount importance to the clinician. For example, are there subgroups of patients who may benefit more than others? Are all β blockers equivalent in their effect in secondary prevention? What is the optimal dose? In addition, the β-blocker trials were completed for the most part before the widespread use of aspirin as a secondary prevention agent, and it is not known whether the protective effects of aspirin and the β blockers are additive, although theoretically this seems likely. Similarly, it is not known whether the early use of a β blocker increases the protective effect of thrombolytic agents.

Early or late treatment? Despite the evidence from the ISIS-1[9] and MIAMI[8] trials that early treatment with an intravenous β blocker reduces mortality, this treatment modality has not become routine practice in the United Kingdom or in many other European countries. There are probably 2 reasons for this. First, both trials included very low-risk patients (placebo group mortality rates in ISIS-1 and MIAMI were 4.5 and 4.9%, respectively); because the true overall mortality rate of patients admitted to the hospital with suspected myocardial infarction is 3 or 4 times higher than this, most clinicians are unsure if the results of the trials really apply to the patients they see in routine practice. Second, the MIAMI trial results only apply to a small proportion of the patients admitted to the participating hospitals (5,784 patients included out of 26,439 admitted), and it is not immediately obvious to a clinician how to select patients for treatment in the way that was used in the trial. Moreover, it is not known how the 16,027 patients included in ISIS-1 were selected, since no register of excluded patients was kept. Crude calculations suggest that each center was only randomizing 1 or 2 patients per month; thus, some special form of selection may have been occurring inadvertently. Thus, because early β-blocking therapy might be harmful in certain patients, most clinicians in the United Kingdom do not begin prophylactic treatment until after the acute stage of the infarction.

Which patients should be treated? Since the results of clinical trials apply only to patients similar to those who fulfilled the inclusion and exclusion criteria established in the protocol, information is not available about the effect of β blockers on infarct survivors with conditions normally considered to be contraindications for treatment, such as asthma and heart failure. As noted previously, there is a low mortality rate in the placebo groups of many of the secondary prevention trials, but without knowing the fate of patients excluded from these trials, it is difficult to be certain of the significance of these figures. The trial of early nifedipine in acute myocardial infarction (Trent study)[12] was the only large postinfarction study in which a register of excluded patients was maintained and all of these patients were followed for the duration of the study. The mortality rates in the patients randomized to placebo or nifedipine treatment were 6.3 and 6.7%, respectively, but in the excluded patients, the mortality rate was 18.2%. Therefore, the Trent study applies only to patients at low risk, and it seems likely that the same is true of all the β-blocker trials.

Some, but not all, of the β-blocker trials excluded elderly patients. Few trials attempted to define any particular type of patient for inclusion, although the propranolol study by Hansteen et al[10] set out to include only those at high risk. Therefore, attempts to identify special groups of patients who might particularly benefit from or be harmed by β-blocking therapy depend on subgroup analyses of the published trial, which is always an unreliable process. The problem is that the more subgroups that

FIGURE 6. Beta blockers after myocardial infarction: relation between point estimates of relative risk reduction or increase and the placebo mortality rate.



are constructed within which to compare the effects of treatment, the greater the likelihood that an apparently "significant" difference will occur by chance. In general, subgroup analysis should only be used as a means of generating hypotheses that can be used as a basis for subsequent trials. In fact, subgroup analysis of the β-blocker trials does not identify any patient group that should be treated differently: patients of all ages as well as with all sites of infarction as documented by the electrocardiogram seemed to benefit equally from treatment.

Thus, the principal difficulty is to decide whether patients at low or high risk should be treated. Since the prognosis in low-risk patients—the young and those with a first infarction—is good, it may not be useful to treat them, especially in light of the adverse effects that may occur, such as lethargy, muscular aches and pains, cold extremities and impotence. On the other hand, patients at high risk—the elderly, those with multiple previous infarctions and those with poor left ventricular function—may be harmed by β-blocking therapy by the induction of heart failure, in addition to the adverse effects of these drugs.

Subset analysis of the β-blocker trials in terms of likely risk has also proved unhelpful. In the Norwegian timolol trial,[4] the overall relative risk reduction was 36%, whereas in the subgroup with a previous infarction it was 21%. In other subgroups considered to be at high or low risk, the relative risk reductions were 40 and 53%, respectively. Similarly in BHAT,[5] the overall risk reduction was 26%, whereas in the subgroup with a previous infarction it was 18%, and in those who were considered to be at high or low risk, it was 30 and 27%, respectively.

Figure 6 summarizes the relation between the trial results and the risk of the patients included by relating the relative risk reduction (or increase) associated with active treatment to the placebo mortality rate seen in each of the main trials. It has been assumed that the placebo rate indicates the degree of risk of the patients included. Although Figure 6 indicates a trend suggesting increasing benefit from β blockers with increasing patient risk, this is far from statistically significant. Thus, a β blocker seems to be indicated for most patients who survive a myocardial infarction, although treatment should be withdrawn immediately in low-risk patients who experience troublesome adverse effects.

Which beta blocker? Among the late entry trials, both timolol[4] and propranolol[10] have been shown to reduce mortality, although it is likely that all β blockers are effective in secondary prevention after myocardial infarction. Clearly, practicing clinicians will prefer an agent with proven efficacy and a simple dosage regimen; in the study cited previously, timolol was shown to be effective at doses of 5 to 10 mg twice daily.

CONCLUSIONS

Despite their beneficial effects in angina, calcium antagonists have no preventive effect in patients with myocardial infarction. Meta-analysis of trials of secondary prevention appears to indicate that β blockers are effective in reducing mortality in patients with myocardial infarction, although to date, there are no data to suggest that either high- or low-risk patients in particular will benefit from treatment, nor that the ancillary properties of different drugs in this class are significant in reducing mortality. Therefore, β blockers are generally warranted for most patients who survive a myocardial infarction, although clinical practice and recommendations regarding a particular drug or dose must be made according to the present condition and past history of each patient. Additional information in this clinical setting will not be available until the relevant clinical trials are conducted.

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Advantages of Beta Blockers Versus Antiarrhythmic Agents and Calcium Antagonists in Secondary Prevention After Myocardial Infarction

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Patients who have sustained ≥1 myocardial infarcts are at high risk for sudden death or reinfarction; the risk is highest for those with lowest ventricular ejection fraction, continuing myocardial ischemia and asymptomatic high-density and complex premature ventricular contractions. At present, β blockers when given prophylactically are the only agents that reduce the incidence of sudden death and reinfarction in survivors of myocardial infarction (MI) in the first 2 years. The beneficial effect was shown to correlate with a reduction in heart rate, the effect being absent or deleterious with β blockers with marked sympathomimetic activity. The effects of β blockers on ventricular fibrillation appeared to be dissociated from those on premature ventricular contractions. Trials with calcium antagonists indicate that these drugs had no effect or increased the mortality rate. The divergent effect of β blockers and calcium antagonists is unexplained but may be due in part to a lack of bradycardiac effect of calcium antagonists; there were no differences in effect among different calcium antagonists. Data from trials involving class I antiarrhythmic agents indicate that agents acting by depression of cardiac conduction are either devoid of effect or produce a modest increase in mortality. Results of the Cardiac Arrhythmia Suppression Trial, employing the newer class I agents flecainide and encainide, were used to determine whether the suppression of premature ventricular contractions in the survivors of acute MI reduces mortality. Flecainide and encainide suppressed premature ventricular contractions >80%, but resulted in an increased mortality rate undoubtedly due to a marked proarrhythmic effect. Whether these data can be extrapolated to all class I agents is uncertain. Preliminary data with class III antiarrhythmic agents suggest that these agents, especially amiodarone, similarly to β blockers, have the potential to reduce mortality in survivors of MI. Evolving data suggest that in the secondary prevention of morbid events in the survivors of acute MI, the focus must shift away from antiarrhythmic agents that delay conduction and toward β blockers and antifibrillatory actions resulting from a prolongation of refractoriness.

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Coronary artery disease continues to be the leading cause of death in technically advanced countries: in the United States alone, approximately 450,000 persons succumb to sudden death each year.[1] Cardiac arrest in these cases is generally initiated by ventricular tachycardia that deteriorates into ventricular fibrillation.[2] Most persons who have cardiac arrest have a history of previous myocardial infarction (MI). This subset of patients, comprising those with clinically identifiable correlates of MI, as well as those experiencing essentially silent myocardial necrosis,[3] probably form the largest group susceptible to high risk for sudden cardiac death.[4]

Three major factors are considered to be the critical determinants of risk: (1) reduced ventricular function[5] reflecting the overall size of infarct or infarcts, (2) persisting latent or manifest myocardial ischemia,[6,7] and (3) the presence of the so-called potentially malignant ventricular arrhythmias[5,8,9] that result from electrical instability. These abnormalities appear to provide the milieu for the development of sudden death in persons who have a history of MI. Unless the reduced ventricular function stems directly from "chronic ischemia" rather than from irreversibly damaged myocardium, pharmacologic therapy is unlikely to improve the ventricular ejection fraction. On the other hand, numerous antiarrhythmic and antiischemic agents have been assessed to determine whether the mortality rate might be reduced by pharmacologic therapy in the survivors of MI by reduction of ischemia, arrhythmias or both.

A meta-analysis of the effects of various subcategories of class I antiarrhythmic agents, β blockers and calcium antagonists is likely to provide insight into the mechanisms whereby the occurrence of sudden death among those who have survived acute MI might be reduced. Data on the effects of class III agents are limited. Pooled data analyzed by Furberg[10] are presented in Table I. The results permit tentative inferences and conclusions regarding the potential advantages and disadvantages of various electrophysiologic classes of antiarrhythmic

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TABLE I Retrospective Evaluation of Randomized Antiarrhythmic Trials

Class	Randomized Patients (active/placebo)	No. of Deaths (active/placebo)	
Type Ia	1642/1563	122/112	
Type Ib	6177/6076	196/150	
Type Ic	1278/1117	97/65	
Total	9097/8756	415/327	(+22%)
Type II			
Short-term	13,815/13,721	513/586	(−14%)
Long-term	12,140/11,551	917/1090	
Type III*	204/193	22/20	(+4%)
Type IV	8870/8887	873/825	(+6%)

* Note that the number of patients for class III agents is small and does not include a figure for trials with amiodarone, which are, for the most part, ongoing.
Adapted from *Am J Cardiol.*[10]

agents and their role in reducing mortality in the survivors of acute MI.

A new perspective is emerging in the wake of the report of the findings of the Cardiac Arrhythmia Suppression Trial.[11] This article reports on the current status of such a perspective by critically reviewing the data from trials that indicate a benefit from treatment and those that show either no benefit or a deleterious effect on the occurrence of sudden death in the survivors of acute MI. The potential significance of heart rate reduction by adrenergic blockade or by specific bradycardic agents influencing the fibrillatory properties of the ischemic myocardium is emphasized.

BETA BLOCKERS IN SECONDARY PREVENTION OF MYOCARDIAL INFARCTION

The prophylactic administration of β blockers to the survivors of acute MI has generated a great deal of interest during the past 20 years. When therapy with these drugs is commenced between 4 and 28 days after an acute MI and continued for ≥90 days, there is a consistent and highly significant reduction (18 to 39%) in sudden cardiac death and a decrease in the reinfarction rate of between 35 and 40%[4,12–14] in the first year. The reduction in mortality occurs regardless of age, sex, race, site of infarction or comparative risk profile of the patients; however, as might be expected, the beneficial effect is more readily demonstrable in those at highest risk for a coronary event. This is particularly striking in the case of post-MI patients with markedly reduced ventricular function.[15]

Pooled data from 18,000 post-MI patients in randomized trials reveal an average reduction in mortality of approximately 20%.[4] The exact details of individual trials are presented elsewhere in this symposium. The reduction in sudden death by β blockers was even more striking than reduction in total mortality: approximately 30% (95% confidence limits of 20 to 40%).[4] With the exceptions of aspirin and aspirin-like drugs, β blockers are the only agents that have been shown to reduce the incidence of sudden death in controlled clinical trials. An understanding of the precise mechanisms mediating their beneficial effects on mortality is clearly important in the development of newer pharmacologic strategies. Because drug therapy of any kind is unlikely to alter substantively the level of ventricular dysfunction that results from blighted myocardium, the role of other factors needs to be considered as the basis for the salutary effects. Two are of particular importance: the first relates to the actions of these agents on the electrical instability occurring independently of ischemia and the other stems from the effects of β blockers on myocardial ischemia and its hemodynamic and metabolic determinants.

Significance of suppressing ventricular arrhythmias as a mechanism: That adrenergic transmitters play a significant role in the genesis of ventricular arrhythmias has been recognized for many decades.[16] For example, reserpinization of experimental animals prevents the development of ventricular fibrillation due to cardiac glycoside intoxication in experimental animals.[16,17] It has also been found that regional cardiac sympathectomy[18] and left stellate ganglionectomy[19] control recalcitrant ventricular arrhythmias in humans. It is therefore assumed that antiarrhythmic actions of β blockers stem directly from their ability to reverse the deleterious electrophysiologic effects of catecholamines. In recent years, β blockers have gained prominence as antiarrhythmic agents, especially in reducing the incidence of sudden cardiac death in the survivors of acute MI[12–14] and in the control of recurrent ventricular fibrillation or torsade de pointes in patients with the long QT_c interval syndrome.[20] However, it is far from clear whether the reduction in sudden death by β blockers in the survivors of acute MI results simply from suppression of asymptomatic ventricular arrhythmias. There are, nevertheless, numerous studies indicating that most β blockers have a significant suppressant effect on premature ventricular contractions in patients with and without cardiac disease.[21] The effect is characterized by: (1) a significant effect in approximately 50% of the patients in various series; (2) a higher degree of suppression with respect to the higher grades of premature ventricular contractions, especially runs of ventricular tachycardia; and (3) abolition or a marked attenuation of the circadian pattern of distribution of premature ventricular contractions, when present.

There are, however, a number of reasons why it is unlikely that the beneficial effect of β blockers on sudden death in survivors of MI is mediated via the suppression of premature ventricular contractions. Only approximately 12 to 30% of those patients have complex ectopic activity, especially runs of ventricular tachycardia, during the post-MI period.[22] Thus, in the various β-blocker trials a relatively small number of patients with the so-called potentially life-threatening ventricular arrhythmias would have been included. The observed benefit must have occurred independently of effects on premature ventricular contractions. It has been reported that premature ventricular contractions tend to increase from the early hospital phase to approximately 6 weeks after MI in patients on placebo. On β blockers, this tendency was blunted somewhat but not dramatically reduced.

A formal analysis of the influence of arrhythmia suppression in the Beta-Blocker Heart Attack Trial[23] showed that patients without arrhythmia derived as much benefit from the β blocker as did those who exhibited arrhythmia on Holter recordings. Similarly, in the metoprolol study,[24] the β blocker had no suppressant effect on premature ventricular contractions but significantly reduced the occurrence of ventricular fibrillation. Thus, it appears unlikely that such an effect on premature ventricular contractions might lead to a significant reduction in sudden death. Even with more powerful suppressant agents, as assessed in the Cardiac Arrhythmia Suppression Trial,[11] a reduction in sudden death in this subset of patients has not been reported. This issue is discussed further later in this article.

Beta blockade and ventricular fibrillation threshold: Unlike the Cardiac Arrhythmia Suppression Trial, the β-blocker trials were not suppression trials; effects on arrhythmias were not evaluated. When the drugs were given intravenously early in the course of infarction, the frequency of occurrence of ventricular fibrillation was significantly reduced.[23,24] Norris et al[25] showed that propranolol, administered at approximately the time of presumed coronary occlusion and subsequently continued, significantly reduced the incidence of ventricular fibrillation in the hospital, compared with the effects of matching placebo. A similar observation was made in the metoprolol study.[24] For example, there were 17 cases of ventricular fibrillation in the placebo group of 697 patients, but only 6 episodes in the β-blocker-treated group of 698 patients ($p < 0.05$). Again, there was no significant effect on premature ventricular contractions. Clearly, the antiectopic effects of β blockers were dissociated from their antifibrillatory actions. It is known that ischemia and catecholamines lower the ventricular fibrillation threshold; β blockers might abort sudden death by elevating it.[26] On the other hand, a favorable change in ventricular fibrillation threshold is unlikely to be the sole basis for the observed beneficial effect induced by β blockers. As discussed later, many agents (such as class I antiarrhythmic compounds and calcium antagonists) consistently elevate the ventricular fibrillation threshold but have little or no effect on sudden death and may even increase its occurrence in patients with MI. Reduction in heart rate accompanying an increase in the ventricular fibrillation threshold appears to be a modulating factor of potential importance.

Favorable effect of beta blockade on sudden death relative to reduction in heart rate: In the β-blocker trials, the benefit of β blockers could not be correlated with their associated properties of cardioselectivity or local anesthetic actions. However, the observed benefit appeared to be correlated negatively with their sympathomimetic actions as reflected in the degree of reduction in resting heart rate. Indeed, reduction in heart rate is the common denominator in the salutary effect of β blockers on sudden death and reinfarction rate in patients surviving MI. Kjekshus[27] carried out an analysis of the most significant β-blocker trials in the survivors of acute MI; he found that a linear correlation existed between the degree of heart rate reduction effected by a β blocker and the percentage reduction in sudden death during chronic prophylaxis with the compound (Fig. 1). It was of interest that only those β blockers that reduced heart rate significantly were effective.

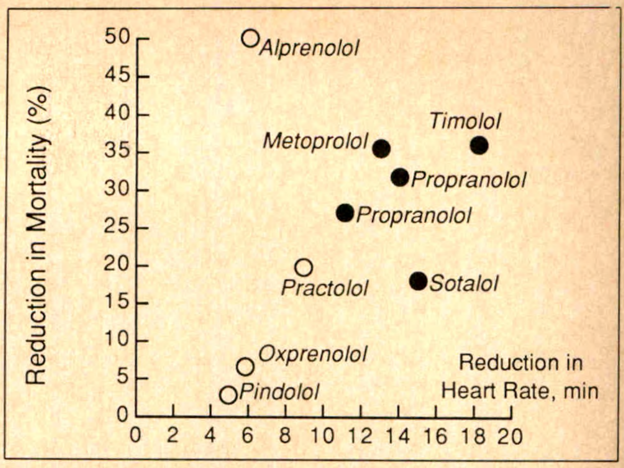

FIGURE 1. Relationship between heart rate reduction and reduction in mortality induced by β blockers in survivors of acute MI. Note that β blockers that have significant intrinsic sympathomimetic activity with little or no bradycardic effects exert little or no effect on mortality. (Reproduced with permission of *Am J Cardiol.*[27])

In contrast, β blockers with marked intrinsic sympathomimetic activity and little or no bradycardic response at rest either had no effect on sudden death or increased its incidence. For example, drugs that have significant sympathomimetic activity, such as pindolol or oxprenolol, either had no effect or were deleterious. The effects of β blockers with marked sympathomimetic effect (e.g., pindolol) on ventricular fibrillation threshold are not known.

It is of interest that other causes of bradycardia might also exert antifibrillatory effects. For example, 1 study showed that in rabbits made hypothyroid, ventricular fibrillation threshold was significantly elevated compared with euthyroid controls and markedly reduced in rabbits made thyrotoxic by thyroid hormone injection.[28] In that study, the changes in ventricular fibrillation threshold were correlated inversely but significantly with heart rate. It is also known that reduction of heart rate to levels below control by vagal stimulation has antifibrillatory effects.[29] Scherlag et al[30] found that vagal stimulation abolished arrhythmias during coronary occlusion in an open-chest canine model of experimental infarction. These observations indicating an inverse correlation between the occurrence of ventricular fibrillation and heart rate are likely to have important clinical implications. They emphasize the importance of slow heart rate in maintaining electrical stability in the ischemic myocardium.

What might be the "ideal" heart rate for patients with various ischemic myocardial syndromes nonetheless remains essentially a matter for conjecture. Before the days of routine β-blocking therapy, Norris et al[31] showed that in post-MI survivors the average heart rate at the time of hospital discharge was an important determinant of prognosis: those with lower heart rates had better survival during follow-up. It is also known that the circadian rhythmicity in sudden death closely parallels that of heart

TABLE II An Overview of Mortality in Trials Evaluating Calcium Antagonists After Myocardial Infarction

Agent (no. of studies)	No. of Deaths/No. of Patients Active	Control	Observed to Expected	Variance
Acute, short-term studies				
Verapamil (1)	0/8	2/9	−0.9	0.5
Nifedipine (4)	171/2509	157/2521	+7.5	76.7
Diltiazem (1)	11/287	9/289	+1.0	4.8
Subtotal (6)	182/2802	168/2819	+7.6	82.0
Long-term studies				
Nifedipine (1)	66/1140	64/1139	+1.0	30.7
Lidoflazine (1)	177/896	168/896	+4.5	69.7
Subtotal (2)	243/2036	232/2035	+5.5	100.4
Acute and long-term studies				
Verapamil (1)	149/1729	145/1718	+1.5	67.2
Total (9)	574/6567	545/6572	+14.6	249.6

Typical odds ratio of 1.06; 95% confidence interval of 0.94 to 1.2, not significant. Reproduced with permission of *Cardiovasc Drug Ther.*[52]

ate and catecholamine discharges.[32] Fewer deaths occur etween midnight and 8 A.M. The effects of propranolol on he circadian rhythmicity was examined by Peters et al[33]; ropranolol had a variable effect on the incidence of udden death between 8 A.M. and 11 P.M. In contrast, it roduced a striking decrease on the incidence of sudden eath between the hours of 2 A.M. and 8 A.M. (Fig. 2), ndoubtedly coincident with the most pronounced bradyardic response, again emphasizing the significance of owering heart rate in post-MI patients. It should be mphasized that the exaggerated reduction in heart rate bserved with β-blocking therapy in the early hours of the norning might be due in part to a vagal dominance reulting from the block of sympathetic impulse traffic to he sinus node. This suggests that the slowing of heart ate by interventions that reduce the action of sympathetc transmitters to the heart might be beneficial in the etting of acutely or chronically ischemic myocardium, in art by augmenting vagal activity, which has been demnstrated to be associated with an antifibrillatory activity n the ventricle.[30]

Potential role of antiischemic effects of beta blockade in mediating a reduction in sudden death: Both calcium antagonists and β blockers have been tested for their cardioprotective effects in survivors of acute MI. There is convincing in vitro and in vivo experimental data that β blockers and calcium antagonists exert significant cardioprotective effects in the ischemic myocardium[16–19,26,33–49] and beneficial effects on ischemic ventricular arrhythmias.[16,17,38] These drugs have been shown to reduce myocardial infarct size,[42,47,48] improve segmental ventricular wall motion abnormalities[49] and elevate ventricular fibrillation threshold.[26,44] With open-chest canine as well as closed-chest canine models of experimental myocardial ischemia, calcium antagonists significantly increased endocardial perfusion[43,49]; β blockers also achieved a significant, although less striking, effect on endocardial perfusion.[49] Numerous experimental studies indicate a ed beneficial effect of calcium antagonists in ventricular reperfusion arrhythmias[50] as well as in the model of "stunned" myocardium.[51] Consistent with these experimental data are the findings from extensive clinical studies with subjective and objective end points that indicate both calcium antagonists and β blockers exert equipotent or close to equipotent antiischemic effects in patients with coronary artery disease. Thus, if net effect on MI were the predominant mechanism to account for the beneficial effect of β blockers in curtailing sudden death in the survivors of acute MI, then calcium antagonists might be expected to exert comparable efficacy in this setting.

CALCIUM ANTAGONISTS AND CARDIOPROTECTION: SIGNIFICANCE OF THEIR VARIABLE EFFECT ON HEART RATE

There is a compelling reason for calcium antagonists to exert a favorable effect on sudden death by ameliorating ischemia in the survivors of acute MI. Surprisingly, data reported to date have been negative, have been inconclusive or have demonstrated a potentially deleterious effect.[52] For example, the results with verapamil, the first calcium antagonist investigated for its effect on reducing mortality and reinfarction rate in MI survivors, are inconclusive.[53–56] In that study, 717 patients were treated with verapamil and 719 were treated with placebo. At the end

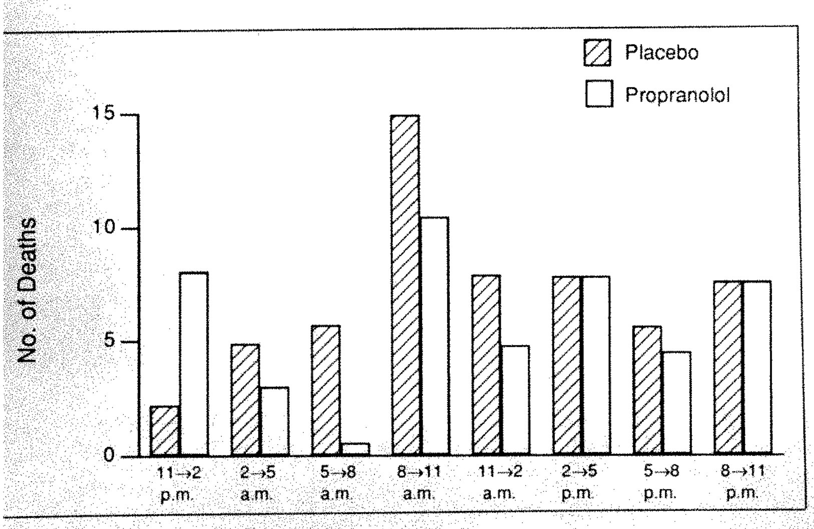

FIGURE 2. Circadian rhythmicity in the occurrence of sudden death in the Beta-Blocker Heart Attack Trial. Note, that the effects of propranolol are greatest at a time when the heart rate is lowest. (Reproduced with permission of *Am J Cardiol.*[23])

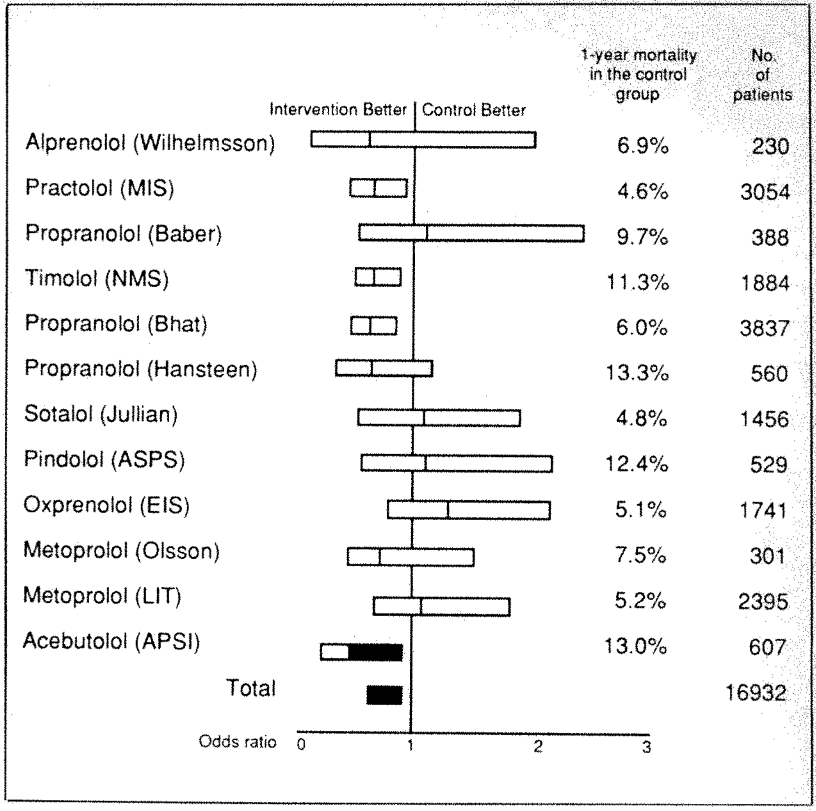

FIGURE 3. Typical odds of 1-year mortality for trials and by numbers of patients and by the types of β blockers given to patients surviving acute MI. The trials are designated by contractions of their names or by the first author. Not all the trials have been mentioned in the text. Note the overall favorable impact of β blockade on mortality in survivors of acute MI. APSI = Acebutolol Prevention of Secondary Infarction; ASPS = Australian and Swedish Pindolol Study; Bhat = Beta-Blocker Heart Attack Trial; EIS = European Infarction Study; LIT = Lopressor Intervention Trial; MIS = Multicentre International Study; NMS = Norwegian Multicenter Study.[12,13,63–72]

of 6 months, the mortality in the treated group was 12.8% vs 13.9% in the placebo series. At 12 months, the corresponding figures were 15.2% vs 16.4%. Although a trend in mortality reduction was evident, it is clear that the drug, given early, did not significantly reduce early mortality from acute MI.

Yusuf and Furberg[52] recently reviewed most of the randomized trials of calcium antagonists after acute MI. Table II shows data summarized from 9 randomized controlled trials that involved 13,139 patients.[52] It was noteworthy that 8 of the 9 trials showed a small excess of mortality in the treated group, although the difference from placebo was not statistically significant. There were 574 deaths among the 6,567 patients randomized to the active treatment group (8.7%); in the control group there were 545 deaths in a population of 6,572 (8.3%). This gave an odds ratio of 1.06 with 95% confidence interval 0.94 to 1.20. The results were similar when the data were separated into 2 groups based on the time at which treatment was initiated, either soon after or 1 to 2 weeks after MI.

It was of interest that a nonsignificant excess in mortality was consistently observed with all calcium antagonists.[57-61] Data on verapamil (1 trial with 3,464 patients),[57] lidoflazine (1 trial with 1,792 patients)[60] and nifedipine (5 trials with 7,309 patients) are derived from reasonably large population samples, although the data on diltiazem are limited (only 576 patients in 1 trial).[59] Thus, the potential beneficial effect of diltiazem on mortality in patients with MI cannot be excluded. This possibility is of interest, because diltiazem may have the highest potency for reducing heart rate.

Held et al[62] have analyzed results of 28 randomized trials involving 19,000 patients which confirm the lack of effect or potentially deleterious effects of calcium antagonists in patients with acute MI and unstable angina. In contrast to those of β blockers (Fig. 3), trials of calcium antagonists reported 873 deaths among 8,870 MI patients (9.8%) randomized to active treatment. In contrast, there were 825 deaths among 8,889 control patients given placebo (9.3%; odds ratio of 1.06, 95% confidence interval 0.96 to 1.18). There was no evidence of a beneficial effect on the development of infarction, infarct size or rate of reinfarction (Fig. 4). No differences were evident in the overall effects of the different calcium antagonists. The results were similar in the unstable angina trials: 110 of 561 patients treated with calcium antagonists compared with 104 of 548 controls developed MI; 14 of 591 treated patients died, compared with 9 of 578 control patients. Whether the failure of routine administration of calcium antagonists, compared with β blockers, to reduce the risk of initial infarction or death in patients with acute MI or unstable angina might largely stem from lack of a bradycardic effect remains to be determined.

Calcium antagonists exert variable effects on the 24-hour profile of heart rate.[73] The dihydropyridines either have no effect or tend to increase heart rate slightly over 24 hours while preserving its circadian periodicity. In contrast, both verapamil and diltiazem tend to produce a modest decrease (Figs. 5, 6), although their effects do not approach those of β blockers without intrinsic sympathomimetic activity (Fig. 6). A rate-lowering β blocker consistently decreases heart rate markedly and attenuates its circadian periodicity (Fig. 6). Thus, as stressed by Yusuf

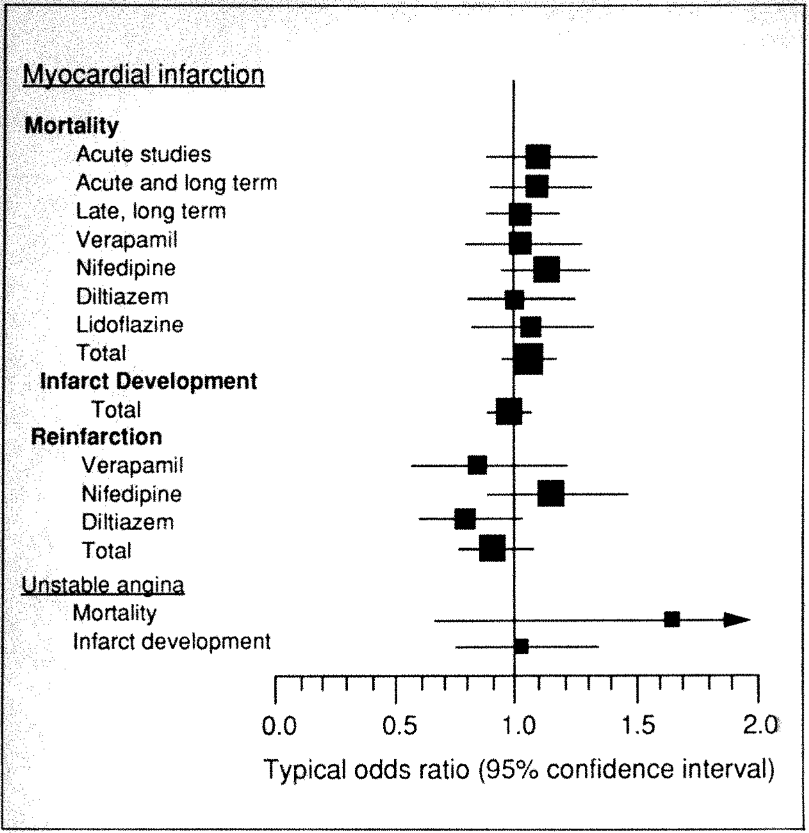

FIGURE 4. Typical odds of death, infarct development and reinfarction by disease, type of trials and drug. Areas of squares are proportional to numbers of patients. Bars indicate 95% confidence intervals. Portions to left of vertical line (corresponding to odds ratio <1) indicate reduced risk with treatment; portions to the right of the vertical line indicate increased risk with treatment. Upper 95% confidence limit for effect on mortality in unstable angina = 6.2. Note that treatment does not seem to reduce risk of any event. (Reproduced with permission of *Br Med J*.[62])

and Furberg,[52] the variable effect of calcium antagonists on heart rate in men may account for the unexpectedly disappointing results on mortality following therapy with calcium antagonists; the data are consistent with the failure of this class of drugs to exhibit unequivocally beneficial effect on infarct size, development of MI or reinfarction in trials of MI or unstable angina.[74]

However, the positive data from the recent trial of diltiazem in patients with non-Q-wave infarction merits consideration.[59] This multicenter, randomized, double-blind trial involved 576 patients recovering from non-Q-wave infarction. Diltiazem (360 mg/day) was given to 278 patients and placebo was given to 289 patients for 14 days after acute MI. The 2 groups were identical. The 14-day mortality rate was similar in both groups, but reinfarction occurred in significantly ($p <0.04$) fewer treated patients. There was a very low incidence of mortality (3%) in both groups, although 61% of patients were treated concurrently with β blockers. The demonstrated salutary effect of diltiazem on reinfarction may be greatest in the presence of β blockade, a finding also noted in trials involving patients with unstable angina[74] in which a calcium antagonist was combined with a β blocker. A major reduction in heart rate is likely during a combination regimen of diltiazem and a β blocker. An analysis of changes in heart rate in patients taking both β blockers and diltiazem vs diltiazem alone relative to the beneficial effect remains to be performed.

An intriguing observation was made in another, larger trial[75] in which 2,466 patients surviving Q- and non-Q-wave acute MI and being treated with or without β blockers were randomized in a double-blind fashion to receive either diltiazem or placebo. Cumulative mortality and reinfarction rates were similar in diltiazem-treated and placebo-treated patients, who were followed for a mean period of 25 ± 8 months. Overall data are shown in Figure 7. Diltiazem had no significant effect on mortality for the entire group. However, when a subset analysis was performed, it was clear that in patients with a history of pulmonary congestion, reflected in a lower ejection fraction, mortality over the follow-up period was increased; in the group without pulmonary congestion, there was a significant reduction in mortality. The reason for the difference is not clear. However, those data are in marked contrast to those with β blockers in which benefit was evident at all levels of function and appeared to be greater in those with cardiomegaly and pulmonary congestion.[15]

Myocardial ischemia and heart rate: significance of specific bradycardic agents: That calcium antagonists do not exert a significant effect in reducing sudden death in the survivors of acute MI does not negate the possibility that the efficacy of β blockers in this regard is mediated at least in part through an action on myocardial ischemia. There are experimental and theoretical reasons for thinking that slowing of heart rate by whatever means might be beneficial in ischemia. As emphasized by Clusin,[29] perhaps the most potent means of modulating the severity of ischemia is through the regulation of heart rate.[76] The major effect of heart rate on ischemia is generally attributed to alterations in myocardial oxygen demand. However, experimental data indicate that changes in oxygen consumption may be less critical than previously be-

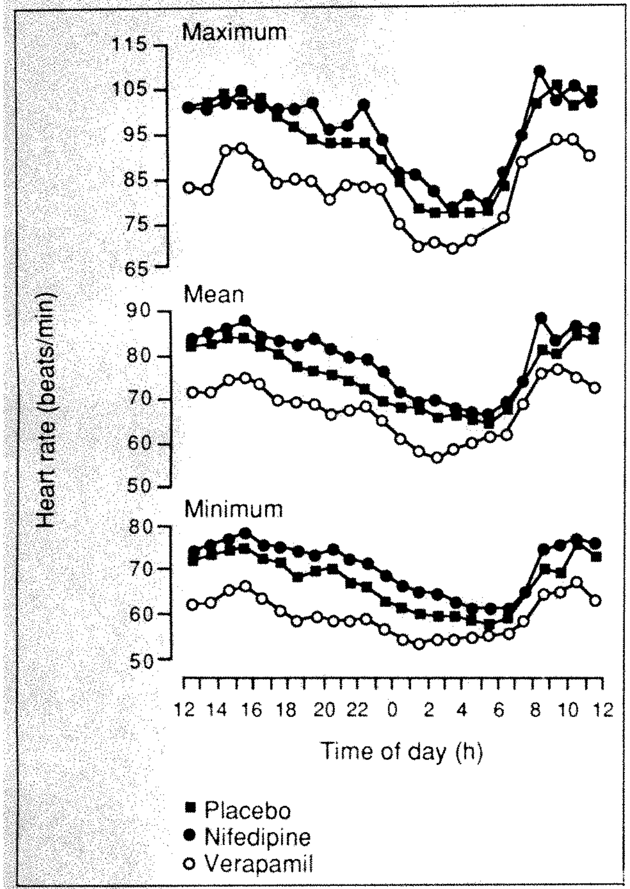

FIGURE 5. The hourly maximum, mean and minimum heart rates during double-blind trial comparing verapamil 120 mg 3 times a day with nifedipine 20 mg 3 times a day and placebo in 28 patients. Note that the circadian rhythmicity in heart rate is maintained; nifedipine tends to increase the heart rate and verapamil tends to slow it, but the mean and maximum heart rates are still high and do not reach the levels induced by β blockade (see Fig. 6). (Reproduced with permission of *Am J Cardiol*.[73])

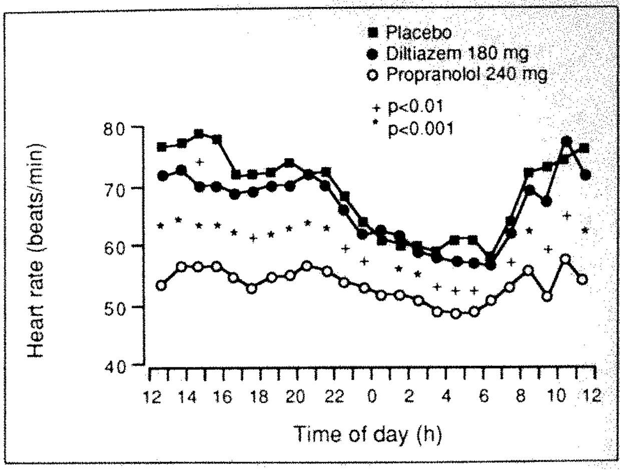

FIGURE 6. The 24-hour ambulatory minimum heart rate on placebo and diltiazem 180 mg/day in 14 patients with stable angina. Note that diltiazem hardly affects the minimum heart rate during the 24-hour monitoring, whereas propranolol 240 mg/day consistently and significantly reduces it. (Reproduced with permission of *Am J Cardiol*.[73])

lieved.[77] The major effect of heart rate may stem from the modulation of calcium influx and retention by the ischemic myocardium.[29] It is known that myocardial calcium channels open and inactivate during each action potential. Therefore, the number of action potentials per unit time will exert a marked influence on calcium ingress. Since Ca^{2+}-Na^{+} exchange over the plateau range of potentials is voltage-dependent, an increase in time at the plateau voltages will have a significant effect on overall cell calcium load.[29] An increase in subendocardial blood flow per minute and per beat in the ischemic zone may also relate, in part, to a reduced number of systolic contractions with a longer period for diastolic perfusion.[78] This may be a mechanism to account for increased subendocardial flow per beat after therapy with a β blocker; the longer diastolic period may also allow for recovery of metabolism per beat, and over successive beats it may contribute to the increased regional contraction in the ischemic zone.[49]

The crucial significance of lower rate as an integral component of the action of β blockade on regional ischemia during exercise is suggested by studies on exercise after β blockade in which the lowered heart rate was returned to the predrug value by atrial pacing.[79] The beneficial effects on blood flow as well as on regional contractile function in the ischemic zone that is evident at lower heart rate were completely abolished at the higher rate produced by pacing.[79] These observations are consistent with a report that the beneficial effect of propranolol in a model of stunned myocardium was negated by atrial pacing at a rate that was identical to the control heart rate.[80]

These findings on the importance of lowering heart rate in ischemia are further emphasized by the use of a specific bradycardic agent (UL FS-49, Thomae Pharmaceutical, Biberach, FRG) in studies in a canine model of chronic coronary artery stenosis.[81] As in the case of β blockade, a marked improvement in the regional function occurred when changes before and after drug administration were compared during exercise; the change was accompanied by a 2-fold increase in subendocardial blood flow.[81] These experimental data on the effects of specific bradycardic agents are of crucial practical importance. These agents constitute pharmacologic probes that may be used to determine the relative importance of the negative chronotropic and inotropic effects in mediating the observed salutary effects of β blockers in the survivors of acute MI and other ischemic myocardial syndromes. If it can be demonstrated that the beneficial effect in terms of electrical stability and amelioration of ischemia stems largely from heart rate reduction, the data will have important therapeutic implications for the treatment of coronary artery disease.

EFFECT OF CLASS I ANTIARRHYTHMIC AGENTS ON SUDDEN DEATH IN THE SURVIVORS OF ACUTE MYOCARDIAL INFARCTION

It is widely believed that the presence of high density or complex premature ventricular contractions in survivors of acute MI constitutes an independent marker of

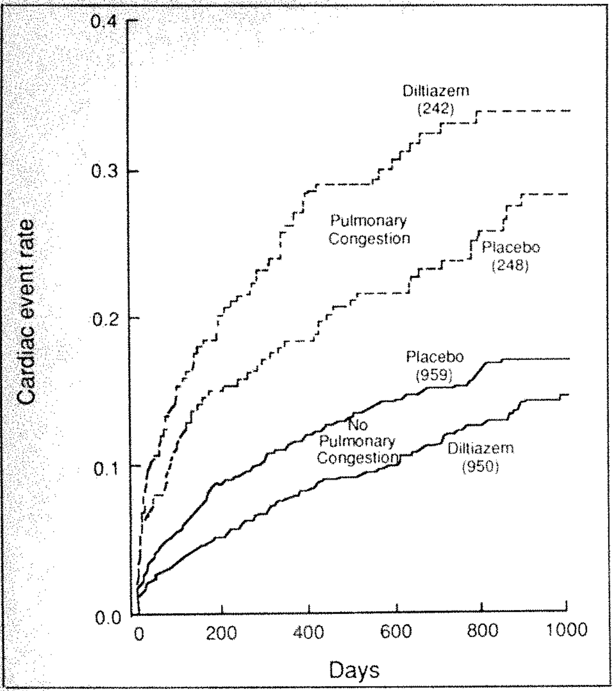

FIGURE 7. Graph showing cumulative coronary incidence according to treatment in patients with and without pulmonary congestion. (Reproduced with permission of *N Engl J Med.*[75])

sudden cardiac death.[5,8] A natural corollary is the presumption that the suppression of such arrhythmias will eliminate the trigger mechanism of ventricular tachycardia and fibrillation. Only in recent years has the availability of antiarrhythmic drugs with the propensity to predictably and significantly reduce premature ventricular contractions permitted the testing of such a possibility.[11,82]

The suppression of premature ventricular contractions is produced predictably by encainide and flecainide: in about 80% of patients, there is >75% suppression of total premature ventricular contractions, >90% suppression of ventricular couplets and almost 100% suppression of ventricular tachycardia beats. The suppressant effect is coincident with the development of conduction delay, as is evident from the progressive lengthening of the QRS interval on the surface electrocardiogram.

Such a degree of premature ventricular contraction suppression is clearly important for 2 reasons. First, it is likely to provide relief from palpitations in the vast majority of patients who have symptoms from extrasystoles. Second, in the asymptomatic patient with complex premature ventricular contractions at increased risk for sudden arrhythmic death, encainide and similar drugs provided the basis for a controlled trial to test the so-called premature ventricular contraction hypothesis: suppression of premature ventricular contractions in the survivors of acute MI will prolong survival. This was the basis for the Cardiac Arrhythmia Pilot Study,[83,84] the purpose of which was to examine the feasibility of a trial to test the premature ventricular contraction hypothesis. The Cardiac Arrhythmia Suppression Trial[11] became the definitive trial whose results were expected to provide information regarding whether suppression of premature ventricular contractions enhances survival in patients at creased risk for sudden death. After 2 years into the study, it appeared that encainide or flecainide increased mortality when compared with the effects of placebo. It should be emphasized that such a strikingly deleterious effect occurred despite >80% suppression of premature ventricular contractions and >90% suppression of runs of ventricular tachycardia.

The results of the Cardiac Arrhythmia Suppression Trial have been extensively discussed,[85] and their implications for the control of sudden death in the survivors will continue to be considered and reappraised in the next few years. In brief, the trial involved 1,500 patients at 23 centers in the United States, Canada and Sweden. Of the 730 patients assigned to encainide or flecainide and treated for an average duration of 10 months, 56 died or had a cardiac arrest, whereas of the 725 given placebo, 23 died or had a cardiac arrest (Fig. 8). The sudden death rate in the encainide or flecainide group exceeded that of placebo by 364% (33 of 730 vs 9 of 725 = 3.64). The trend in mortality was not affected by concomitant therapy with calcium antagonists, β blockers, levels of ejection fraction or any other considered factors. The probability of decreasing the incidence of sudden death with agents that selectively and markedly delay conduction in the treatment of asymptomatic premature ventricular contractions remains unknown. It is likely that the data are applicable to all class Ic agents and possibly to class I agents in general.

These data raise an additional, broader and perhaps a more fundamental issue: that the reduction of premature ventricular contractions may not lead directly to a reduction in sudden death. Continuous monitoring in the setting of a coronary care unit has shown that the onset of ventricular tachycardia, fibrillation or both often is not preceded by significant increases in the numbers and complexity of premature ventricular contractions. It takes only 1 extrasystole to initiate ventricular fibrillation, and a marked reduction in the numbers and complexity of premature ventricular contractions (barring reduction of symptoms when they are present) does not ensure that ventricular fibrillation will be prevented. Moreover, it has not been established clearly what percentage of premature ventricular contraction reduction is needed to effect a meaningful clinical outcome with respect to mortality. Whether drug therapy can in fact eliminate every premature ventricular contraction that is generated in the heart and maintain its effectiveness over prolonged periods is difficult to determine. The percentage reduction of premature ventricular contractions in the Cardiac Arrhythmia Suppression Trial[11] was, of necessity, completely arbitrary, there being no assurance that with a change in the clinical course of patients, which is inevitable, the degree of suppression would not change. As already indicated, the beneficial effect of β blockers on ventricular fibrillation was dissociated from those on premature ventricular contraction reduction.

An analysis of the available data on the effects of various antiarrhythmic agents (exclusive of β blockers) performed by Furberg[10] indicates either an unfavorable

TABLE III Antiarrhythmic Agents and Their Effects on Inducibility of Ventricular Tachycardia, Ventricular Fibrillation and on Premature Ventricular Contractions*

Class	Test Drug	Prevention of Inducibility of VT/VF by PES (% of patients)	Suppression of PVCs by >75% (% of patients)	Suppression of VT beats by >90% (% of patients)
Ia	Quinidine	15–20	60	?70
	Procainamide	15–25	60	?70
	Disopyramide	?	60	?70
Ib	Mexiletine	15	60	>70
	Tocainide	10–15	60	?>70
	Ethmozine	15–20	60	?>70
Ic	Encainide	10–15	80	90–100
	Flecainide	10–15	80	90–100
	Propafenone	10–20	70	90–100
	Indecainide	10–15	70	90–100
II	β blockers	?1–2	50	?70–80
III	Amiodarone	8–40	80	90–100
	Sotalol	40–45	50–60	80
IV	Verapamil	1–2	≤10	≤10
	Diltiazem	?	≤10	≤10

* Data included are crude estimates from controlled and uncontrolled studies reported in the literature. However, they provide a reasonable approximation of the overall effect of various antiarrhythmic agents in affecting 2 major end points used in determining the efficacy of pharmacologic therapy of (life-threatening) ventricular arrhythmias. Note the lack of concordance between suppression of premature ventricular contractions and suppression of inducible VT/VF.

ISA = intrinsic sympathomimetic activity; PES = programmed electrical stimulation; VT/VF = ventricular tachycardia/ventricular fibrillation.

trend with a slight increase in mortality or no effect in survivors of acute MI (Table I). His analysis of the data, taken in conjunction with the results of the Cardiac Arrhythmia Suppression Trial,[11] does not appear to support the use of the clinical end point of suppression of premature ventricular contraction or treatment of asymptomatic arrhythmia as a realistic or desirable approach to the reduction of arrhythmic deaths. As indicated in Table III, there appears to be no systematic relationship between premature ventricular contraction suppression induced by various antiarrhythmic drugs and the prevention of induction of ventricular tachycardia or ventricular fibrillation by programmed electrical stimulation of the heart. A lack of concordance in this regard might indicate that the density and complexity of premature ventricular contractions do not provide reliable information about the electrical instability of the substrate for lethal arrhythmias, as has been widely believed.[5] This issue merits critical reappraisal and scrutiny. In fact, the available data cast serious doubts about whether the presence of premature ventricular contractions in patients with previous infarction does indeed constitute an independent marker of risk for sudden death.

On the other hand, reduction or elimination in repetitive beats by agents that have different electrophysiologic profiles with no effect on conduction (e.g., β blockers) or those with modest depressant effect on conduction (e.g., amiodarone) might be effective in altering mortality in patients with potentially life-threatening ventricular arrhythmias. However, the so-called premature ventricular contraction hypothesis could not be tested with such drugs because they have a complex electrophysiologic profile. Suppression of premature ventricular contraction by these drugs may be only 1 component of their overall pharmacologic effects that contribute to mortality reduction. It remains speculative whether suppression of premature ventricular contraction by β blockers or amiodarone (see later), both exerting significant antiadrenergic actions, contributes to their observed salutary effect on mortality in the survivors of acute MI.

BRADYCARDIA, PROLONGED REPOLARIZATION AND VENTRICULAR FIBRILLATION THRESHOLD: INSIGHTS FROM STUDIES ON AMIODARONE

An interesting observation has been reported by Raine and Vaughan Williams[86] on the changes in the cardiac action potentials in rabbit myocardium that is chronically treated with a variety of β blockers. They

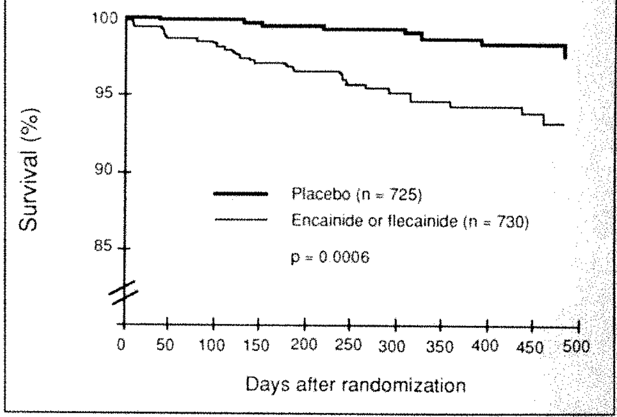

FIGURE 8. Effects of flecainide, encainide and placebo on sudden arrhythmic deaths in the survivors of acute myocardial infarction with high-density premature ventricular contractions. At the end of about 10 months of follow-up, there was an approximately 3-fold increase in mortality on flecainide or encainide despite a substantial degree of suppression of premature ventricular contractions. The excess in mortality in the drug-treated groups compared with the placebo group is due to the proarrhythmic actions of class Ic agents. (Reproduced with permission of *N Engl J Med.*[11])

found that the β blockers propranolol and acebutolol produced a modest but significant lengthening of the action potential duration while not affecting the upstroke velocity of phase 0. It was postulated that such a change represented a physiologic adaptation to chronic sympathetic blockade. The observed prolongation of the action potential was therefore considered a mechanism for the reduction of sudden death by β blockade. The clinical counterparts of these studies have been conflicting. Some studies with the monophasic action potential measurements that used suction electrodes have both confirmed as well as denied the prolongation of repolarization.[87,88] Measurements of the QT_c intervals in humans following long-term β-blocking therapy have shown that repolarization may be shortened, prolonged or not changed at all.[88,89] However, to date, the circadian rhythmicity of QT/QT_c changes induced by chronic β blockade has not been determined. Such a rhythmicity for QT_c is known to be out of phase with the heart rate, being longest when the sinus frequency is the lowest.[90]

Therefore, it is possible that β blockers prolong the QT_c interval but only during the sleep cycle. The effect of homogeneously prolonging repolarization with a corresponding increase in the ventricular effective refractory period might be antifibrillatory and contribute to sudden death reduction in the early hours of the morning. Whether the ventricular effective refractory period increases as a function of long-term β-blocking therapy has not been determined.

A clinical context that resembles the long-term administration of β blockers is the long-term administration of amiodarone. The drug is a complex iodinated molecule that slows the heart rate in a stepwise fashion as a function of time, exhibits significant anti-ischemic properties, antagonizes sympathetic excitation and elevates the ventricular fibrillation threshold.[91] It has a significant effect in suppressing premature ventricular contractions; in both experimental models and in humans it prevents the occurrence of sudden death[91] and is effective when other agents fail in more than two-thirds of patients with life-threatening ventricular arrhythmias. For these reasons, the effects of amiodarone on mortality in survivors of acute MI are of interest.[91-93]

Preliminary data from a recent study are of importance.[94] A population of 312 patients who had survived an MI with complex premature ventricular contractions were randomized into 3 treatment groups. The first group ($n = 114$) was not given antiarrhythmic treatment; the second group ($n = 100$) was given conventional antiarrhythmic treatment with agents and doses adjusted to produce a defined degree of premature ventricular contraction suppression; and the third group ($n = 98$) was treated with an initial loading dose of amiodarone followed by a low maintenance dose of the same drug. The follow-up period lasted 12 months.

By the end of follow-up, there were 15 cases of sudden death in the untreated group, 12 in the group with individualized antiarrhythmic therapy and 5 in the amiodarone group ($p < 0.05$ compared with the untreated group). The data indicate that amiodarone had the potential to reduce sudden death in the survivors of MI, although the number of patients in each group was too small to permit an analysis of the link between sudden death and the degree of suppression of complex premature ventricular contractions. It is likely that, as in the case of β blockers, the beneficial effect is related to the antifibrillatory actions of the drug rather than its antiectopic property.

A number of larger, placebo-controlled trials are being initiated to determine whether the results of this pilot study will be confirmed. Meanwhile, the use of amiodarone in patients who have survived MI and have complex ventricular ectopy cannot be recommended in a routine fashion. In this context, its use must be balanced by awareness of its complex and potentially deleterious side effects relative to the expected beneficial effect on mortality. Nevertheless, the properties of amiodarone and those of β blockers, both significantly attenuating adrenergic stimulation, clearly provide important pharmacologic probes to define the critical determinants of efficacy of a compound for mortality reduction in high-risk survivors of MI. Clearly, the focus must shift from antiarrhythmic agents that delay conduction to those that exert antifibrillatory actions by sympathetic antagonism and those that prolong refractoriness in cardiac muscle.[95-100]

CONCLUSIONS

There now is little doubt that β blockers reduce the incidence of sudden death and reinfarction in the survivors of acute MI. To date, they are the only agents that have been shown in controlled clinical trials to reduce sudden death in patients with MI. However, the precise mechanism mediating their salutary effects is not known. It is likely to be complex and multifactorial, perhaps resulting largely from the competitive attenuation of the ischemic and arrhythmogenic influences of sympathetic stimulation. From the available techniques, it appears difficult to quantify precisely the relative importance of effects on collateral blood flow, myocardial substrate utilization, myocardial oxygen demand, platelet aggregability or even triggers of sustained electrical disturbances in the ischemic myocardium. However, β blockers do not appear to produce their beneficial effect by reducing the number or complexity of premature ventricular contractions. What has emerged from a growing experimental and clinical data base is the key role of heart rate in modulating not only the severity of ischemia, but also the vulnerability to ventricular fibrillation in the ischemic myocardium. The data emphasize the significance of the adrenergic nervous system in mediating the arrhythmogenic potential of the ischemic myocardium.

Despite the fact that calcium antagonists are potent anti-ischemic agents, they appear to have either no effect on sudden death or produce a slight excess in mortality when given prophylactically to survivors of acute MI. For the present, it is difficult to justify their use in the routine prophylactic treatment of survivors of acute MI to reduce sudden death or reinfarction. The divergent effects of β blockers and calcium antagonists on mortality in this setting appear to be related, at least in part, to the variable effects of calcium antagonists on heart rate.

A meta-analysis of controlled trials with various subcategories of class I antiarrhythmic agents suggested either no effect or a modest increase in mortality when those agents were given to survivors of acute MI. The potentially deleterious effect of class I agents on mortality has come into sharp focus with the report from the Cardiac Arrhythmia Suppression Trial that agents that exert a markedly depressant effect on myocardial conduction produce a dramatic increase in mortality despite suppressing premature ventricular contractions in post-MI survivors. The emerging data thus indicate a need for a shift from class I agents and calcium antagonists to β blockers and antifibrillatory antiarrhythmic agents that exhibit antiadrenergic properties for the purposes of secondary prevention in the survivors of acute MI.

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Relevance of Intrinsic Sympathomimetic Activity for Beta Blockers

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Intrinsic sympathomimetic activity (ISA) characterizes a group of β blockers that are able to stimulate β-adrenergic receptors (agonist effect) and to oppose the stimulating effects of catecholamines (antagonist effect) in a competitive way. Partial agonists are ligands that elicit a submaximal response when bound to β receptors at maximal occupancy. In the isolated rat atrium, acebutolol produces a maximal stimulatory effect that is only 17 ± 8% of the maximal effect induced by the full β agonist isoproterenol. The presence of ISA results in less resting bradycardia and less of a reduction in cardiac output than is observed with β blockers without ISA. In the long term, partial β agonists may produce arterial vasodilation and increase arterial compliance, possibly leading to additional beneficial effects in the treatment of hypertension. β blockers with ISA do not have adverse effects on plasma lipoproteins during long-term treatment; in addition, the presence of ISA could counteract the up-regulation of β adrenoceptors often observed with β blockers without ISA. Finally, the presence of ISA has been a conflicting issue for the use of such β blockers in secondary prevention after myocardial infarction. However, the impressive results of the Acebutolol Prevention of Secondary Infarction trial in high-risk patients after myocardial infarction show that acebutolol, a β blocker with moderate partial agonist activity, can be effective in decreasing the postinfarction mortality rate. By exhibiting a strikingly different hemodynamic profile from that of β blockers without ISA, the partial β agonists form an intriguing pharmacologic class of drugs for which prospective clinical trials should be extensively pursued.

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Intrinsic sympathomimetic activity (ISA), or partial agonist activity, characterizes a group of β blockers that can simultaneously stimulate β receptors (agonist activity) and antagonize the effects of catecholamines on these receptors in a competitive manner (antagonist activity). The presence of ISA has been the subject of intense research, and the clinical relevance of this property remains controversial in terms of overall therapeutic efficacy of β blockers, not only in the treatment of angina pectoris and hypertension, but also for secondary prevention after myocardial infarction.

PARTIAL AGONIST ACTIVITY

When bound to β-adrenergic receptors, a β blocker with ISA stimulates the receptors leading to activation of the stimulating guanine nucleotide proteins and of the catalytic adenylate cyclase, and competitively opposes the stimulating effects of catecholamines. When compared with the stimulating effects of a full β-adrenoceptor agonist such as isoproterenol, a β blocker with ISA will elicit only a submaximal response when bound to receptors at maximal occupancy. Abrahamsson[1] has recently shown that partial β agonists cause a concentration-dependent increase in the atrial rate of isolated right atrium of the rat. In this model, acebutolol induced a maximal stimulatory effect corresponding to 17 ± 8% of the maximal effect of isoproterenol. However, when administered before isoproterenol, acebutolol resulted in a right shift of the concentration-response curve of the full agonist, which is characteristic of a competitive antagonist.

Binding sites for β-adrenoceptor agonists may be in high- or low-affinity state, and agonists may either recognize or stabilize a high-affinity form of the β receptor. However, it is not yet known precisely whether partial agonists activate a small percentage of β adrenoceptors into the high-affinity state or if they induce a partial conformational change in all receptors.[2,3]

MAJOR EFFECTS OF INTRINSIC SYMPATHOMIMETIC ACTIVITY

The presence of ISA in a β blocker modifies its pharmacologic effects in a variety of ways. First, cardiac hemodynamics and the effects on peripheral circulation vary according to the extent of the partial stimulation of β receptors. Similarly, the long-term metabolic effects of β blockers are modified in the presence of ISA. Finally, there could be important consequences of partial agonist activity in the regulation of β-adrenoceptor density.

Cardiac hemodynamics: Heart rate (HR) and cardiac output (CO) are less decreased at rest and exercise by

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a β blocker with ISA than by one without ISA. Fitscha et al[4] showed on Holter recordings that the partial agonist activity of pindolol resulted in an increase in nocturnal HR compared with a control period, whereas propranolol, a β blocker without ISA, resulted in a significant decrease in diurnal and nocturnal HR. In patients with ischemic heart disease, the effects of various β blockers on HR and CO at rest after bolus intravenous injections depend on the intensity of partial agonist activity. Svendsen et al[5] showed that propranolol and atenolol, both without ISA, resulted in a dose-related decrease in HR and CO, whereas β blockers with ISA, such as practolol and pindolol, exerted either lesser or no effects on these parameters. In this study, for an equivalent degree of β-receptor blockade assessed by exercise testing, propranolol and atenolol reduced CO by 26 to 28% and HR by 15 to 17%, whereas practolol induced a lesser reduction in CO (12 to 17%) and HR (7 to 10%); pindolol did not modify these parameters.

After long-term treatment, the differences between the hemodynamic effects of β blockers with and without ISA are even more important. In patients with mild-to-moderate essential hypertension treated for 3 weeks, van den Meiracker et al[6] showed that pindolol resulted in a decrease in blood pressure that was associated with decreased vascular resistance (26 ± 6%), whereas the decrease in blood pressure with propranolol was mainly associated with a decrease in CO (11 ± 7%). Atenolol or acebutolol did not significantly modify vascular resistance or CO, although they induced a decrease in mean arterial pressure similar to that resulting from propranolol. In an extensive review comparing the antihypertensive mechanisms of β blockers, Man in't Veld and Schalekamp[7] evaluated the effects of these drugs on CO and total peripheral resistance. After acute administration, β blockers without ISA resulted in the most pronounced decreases in CO and increases in peripheral resistance. In the long term, the effects of these drugs persist, whereas β blockers with moderate ISA (e.g., acebutolol, alprenolol and oxprenolol) induce no additional increase in total peripheral resistance. A β blocker with high ISA, such as pindolol, can even induce vasodilation and a limited increase in CO. Calculated total peripheral resistance is higher after short- and long-term treatment with β blockers without ISA than it is with β blockers with ISA.

Peripheral circulation: Peripheral blood flow is decreased less by a β blocker with ISA than by one without ISA. Relative selectivity for β_1 adrenoceptors can be another factor that could explain why acebutolol did not reduce forearm blood flow at rest in 9 hypertensive patients, whereas this parameter was significantly altered by propranolol for an equivalent cardiac blockade, as shown by Ireland and Littler.[8]

More recently, Levenson et al[9] studied forearm hemodynamics in hypertensive patients treated with acebutolol for 3 months. Using noninvasive techniques (pulsed Doppler velocimetry and strain gauge mechanography), these investigators showed that the partial activity of acebutolol improves forearm arterial compliance by a concomitant decrease in pulse-wave velocity and increase in arterial diameter.

Metabolic effects: The effects of long-term β-blocker treatment on plasma lipoproteins are of major concern during antihypertensive therapy. These drugs can increase plasma triglyceride and very low density lipoprotein cholesterol levels and decrease high-density lipoprotein cholesterol levels.[10] Interestingly, the results of long-term treatment with acebutolol show no adverse effects on plasma lipoproteins.[11]

Beta-adrenoceptor density: The density of sarcolemmal β-adrenergic receptors on cardiac myocytes is regulated by the intensity of sympathetic stimulation or the degree of β blockade. Beta blockers induce an increase in the density of β adrenoceptors, so-called up-regulation. Conversely, stimulation of β adrenoceptors by agonists results in desensitization (down-regulation) of the receptors through phosphorylation of the protein chain of the receptor site on the myocardial cells.[3]

Human lymphocyte membranes are frequently studied in order to measure the density of specific binding sites for radioactive ligands (^{125}I pindolol, for instance) before and after β-blocking treatments. Recently, van den Meiracker et al[6] showed that lymphocyte β-adrenergic receptor density was not significantly modified by 3-week treatment with acebutolol and atenolol in patients with hypertension, whereas it was significantly increased with propranolol and decreased with pindolol. Lymphocyte β adrenoreceptors in humans are of the β_2 subtype. Therefore, the differences observed between the nonselective β blockers propranolol and pindolol are likely to be explained by the presence of ISA for pindolol (resulting in a down-regulation of the β receptors) and the lack of ISA for propranolol (resulting in an up-regulation of the β receptors). The lack of significant modification in lymphocyte β-receptor density observed during atenolol or acebutolol treatment in this study could be explained by the relative β_1 selectivity of both agents. However, the existence of a moderate partial agonist activity for acebutolol could play a role in the absence of variation in β-adrenoceptor density.

To date, no study has clearly demonstrated the lack of effects of acebutolol on cardiac β-adrenoceptor density. However, experimental data on reconstituted β-adrenergic receptors from hamster lung have shown that partial agonists promote less phosphorylation by the β-adrenoceptor kinase than a full agonist such as isoproterenol.[3] These results suggest that partial agonists may cause less desensitization than that associated with saturating concentrations of isoproterenol. It is not known, however, whether the partial agonist activity of acebutolol could counteract an up-regulation of β_1 receptors in cardiac myocytes, resulting in a lack of modification in cardiac receptor density during long-term treatment.

Intrinsic sympathomimetic activity and secondary prevention trials: One of the most controversial issues concerning the presence of ISA has been its clinical relevance for β blockers used in secondary prevention trials. Conflicting results have been observed in previous clinical trials with β blockers with ISA such as alprenolol, practolol, pindolol and oxprenolol. Alprenolol[12] and practolol[13] were able to decrease mortality significantly after long-term treatment following myocardial infarction. However, pindolol[14] and oxprenolol[15] did not show any significant benefit compared with placebo after 2 and 1 years of follow-up, respectively.

In an important and well-documented retrospective meta-analysis, Yusuf et al[16] showed that in late-intervention long-term postinfarction trials, the overall mortality rate was not significantly different between the patients treated by β blockers with ISA (8.4%) and the placebo control groups (9.3%). In contrast, the beneficial effects of β blockers without ISA were obvious, with an overall mortality rate of 7.6% in the treated groups vs 10.5% in the placebo control groups ($p <0.001$). The workers concluded that "there may be important differences between the two classes of β blockers," with a 30% reduction in the odds of death in trials of β blockers without ISA compared with only a 10% reduction in trials of β blockers with ISA. That conclusion, which has been commonly accepted by cardiologists, may have to be reconsidered in light of the results of the Acebutolol Prevention of Secondary Infarction (APSI) trial. In that study, acebutolol, a β blocker with moderate partial agonist activity, decreased the 1-year (318.5-day) mortality rate in high-risk postmyocardial infarction patients by 48%. That result shows that a β blocker with moderate ISA can be effective in secondary prevention. It is not known whether the high ISA of pindolol in one trial[14] or the 320-mg daily dose of slow-release oxprenolol administered in another trial[15] could explain the lack of activity of those compounds in secondary prevention. However, the results of the APSI trial show that the presence of ISA does not preclude any beneficial effect of a β blocker with moderate partial agonist activity in high-risk patients after myocardial infarction.

CONCLUSION

Beta blockers with ISA exhibit a strikingly different hemodynamic profile than do β blockers without ISA. Such partial agonist activity is relevant for long-term treatment of hypertension but, until recently, remained controversial for prophylactic use after myocardial infarction. That conclusion will have to be reconsidered after the impressive results of the APSI trial with acebutolol, a β blocker with moderate partial agonist activity.

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Efficacy of Acebutolol After Acute Myocardial Infarction (The APSI Trial)

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A randomized, placebo-controlled trial was carried out to determine the effectiveness of acebutolol in preventing late death in high-risk patients surviving an acute myocardial infarction (MI). The average 1-year mortality rate in placebo groups of 9 trials of β blockers in post-MI patients was 7.2% compared with 17% in a nonselected cohort of patients who had survived at least 7 days after an MI. The mandate for this trial was based on the fact that high-risk patients whose mortality rate exceeds 20% have not been enrolled in significant numbers in previous trials. It remains to be proved whether β-blocking therapy in this patient population is beneficial. Selection of high-risk patients for inclusion in the trial was based on an algorithm set up from the Essai de Prévention Secondaire de l'Infarctus du Myocarde Registry. At the time of the second interim analysis, the mortality rate in the placebo group was 12%, lower than expected (≥20%). The trial was stopped; at that time, 309 patients had been allocated to placebo and 298 patients to acebutolol therapy. After 318 days, there were 17 deaths in the acebutolol-treated group and 34 in the placebo group, a reduction in total mortality of 48% (p = 0.019). There were 30 vascular deaths in the placebo group and 12 in the acebutolol group. Thus, cardiovascular mortality with acebutolol was reduced by 58% (p = 0.006). The incidence of all cardiovascular-related deaths was lower in the acebutolol-treated group. The total reduction in mortality did not appear to be correlated with secondary risk factors. Although the objective of the study, which was to enroll patients at high risk, was not met, the patients in this trial were at higher risk than average patients in previous trials. We conclude that moderately high-risk post-MI patients can benefit from treatment with β blockers, and β blockers with mild intrinsic sympathomimetic activity can be effective.

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Acebutolol et Prévention Secondaire de l'Infarctus (APSI), a double-blind, placebo-controlled trial of acebutolol following myocardial infarction (MI), was designed to assess the efficacy and safety of acebutolol in high-risk patients after acute MI.[1] It has been reported that the average 1-year mortality rate in the placebo groups of previous late-intervention trials with β blockers is approximately 7%[2]; however, the average 1-year mortality rate of an unselected group of 6,900 patients still alive 8 days after an acute MI was 17% in the Essai de Prévention Secondaire de l'Infarctus du Myocarde (EPSIM) Registry kept between 1975 and 1979.[3] Therefore, the efficacy of β blockers in secondary prevention after an acute MI has been assessed only in low- or moderate-risk patients and not in high-risk patients.

A post-hoc subgroup analysis of the pooled data from the first 9 trials showed that all subgroups of patients benefited from treatment. Subgroups with the presence of high-risk prognostic factors that indicated mechanical or electrical failure benefited the most from treatment.[4] However, even in those high-risk subgroups, the 1-year placebo group mortality rate was <17%, which was the rate reported by EPSIM. Hence, the question of whether high-risk patients, who represent most of the target population, would benefit from β-blocking treatment still remained unanswered.

Approximately two-thirds of postacute MI patients are at high risk, and assuming that it is theoretically possible to select patients at a given mortality risk,[2] the Clinical Pharmacology and Therapeutic Committee of the French Society of Cardiology initiated a randomized trial of β-blocking treatment in patients with a mortality risk of at least 20% during the first year after an MI. The APSI study was intended to include only high-risk patients, i.e., those with a mortality risk ≥20%. The protocol was accepted independently by both the Ethics Committee of the Claude Bernard University and the Ethics Committee of the French Society of Cardiology.[1]

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*See Appendix.

MATERIALS AND METHODS

APSI was carried out in 44 university and community hospitals throughout France. As defined in the protocol, the primary end point assessed was total mortality and cardiovascular death was the second. Vascular death was defined as any death that could be related to a cardiovascular event: sudden death, MI, cardiac failure, stroke or cerebral hemorrhage. Nonfatal events not reported in regular study forms were not identified (i.e., no notification procedure was established during the trial). Hence, the frequencies of nonfatal clinical events are probably incomplete. This also applies to symptoms or signs noted during the follow-up period. The analysis for primary and secondary end points was performed on an intention-to-treat basis. Patients were randomized centrally to receive either acebutolol 200 mg twice daily or matching placebo on average 11 days after onset of symptoms.

High-risk patients were selected on the basis of previous investigations of the EPSIM Registry.[2] Analysis of this registry revealed that by including only patients with ≥6 secondary risk factors, a 1-year mortality rate of at least 20% in the placebo group could be expected.

Patients were eligible if: (1) they had at least 2 of the 3 classic signs of MI (i.e., typical chest pain of at least 1 hour in duration, typical Q waves and significant release of cardiac enzymes); (2) they had been admitted for acute MI >2 and <22 days before; (3) they presented at least 6 of the secondary risk factors of the selection algorithm, including at least 1 "major" secondary risk factor (i.e., prior documented MI, history of dyspnea when walking on flat ground, documented atrial fibrillation, ventricular fibrillation, ventricular tachycardia, overt heart failure or sinusal tachycardia during the reference event, recurrent MI or angina pectoris before day 8). Eligible patients were then checked for exclusion criteria, including transient exclusion criteria, such as heart rate <45 beats/min, complete auriculoventricular block and acute heart failure requiring treatment with at least 2 drugs of different classes, such as diuretic and vasodilator. If the condition disappeared before day 22, the patient was included. Exclusion criteria were contraindication to β-blocking treatment, noncardiac disease with poor prognosis, inability to participate, indication for β-blocking treatment, age >75 years (exclusion criterion dropped 7 months after beginning of patient recruitment), death, malignancy, valvular disease, coma, asthma, chronic bronchopneumopathy, Raynaud's syndrome, participation in another study or previous enrollment in APSI.

A total of 607 patients were randomized and followed for an average duration of 318 days. A registry was kept throughout the trial in 7 centers to assess the proportion of included patients and the 1-year mortality rate of the target population. As shown in Figure 1, less than 12% of the target population was randomized.

The study was organized as a prospective multicenter trial. The Coordinating and Data Handling Center was in charge of managing the trial, editing collected data, controlling compliance by both investigators and patients, randomizing the treatment through an on-line computerized procedure and analyzing the results. The Policy Board decided to monitor total mortality data with a 1-tailed group sequential plan. Interim analyses were scheduled after every 20 deaths. The global first kind statistical error risk was kept at 0.05. The Policy Board was responsible for monitoring the relevance of the study sample to the target population. Its voting members were not otherwise involved in the trial and had no connection with the sponsor. Only the voting members of this Committee and 4 individuals in the Coordinating Center were aware of the interim results. The Critical Events Committee met periodically to classify causes of death. Its members were not otherwise involved in the trial and were kept blind regarding the study treatment.

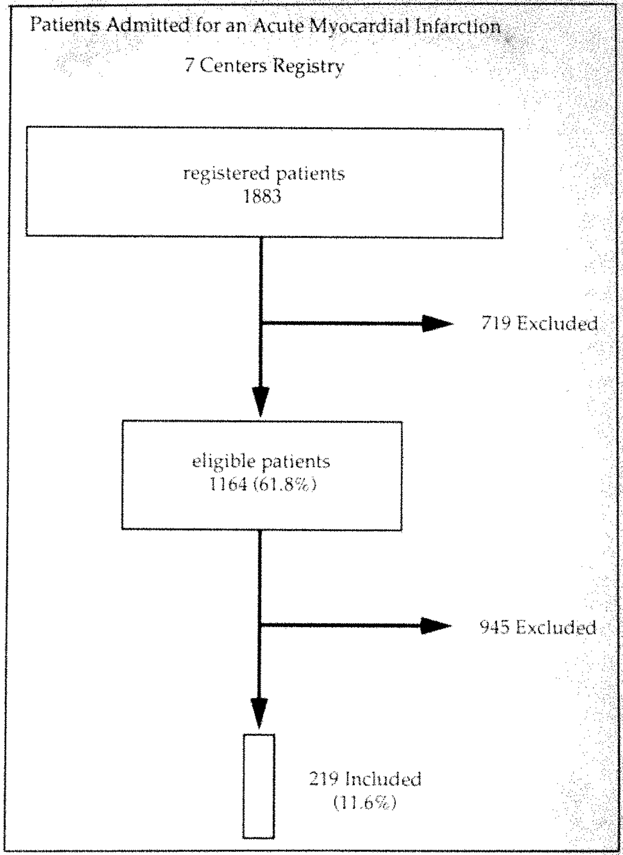

FIGURE 1. Registry of patients admitted for acute MI in 7 centers.

Chi-square test, or Fisher exact test when a theoretical number was lower than 5, was used to compare rates. A Student's t test or analysis of variance was used to compare continuous data. Cox regression was used to adjust the mortality rate difference to delay of survey and baseline variables. The Mantel-Haenszel procedure was used to account for qualitative baseline variables. Homogeneity of relative risks according to the values of binary baseline variables was tested by the Breslow-Day method.[5]

RESULTS

Patient enrollment began in April 1987. At the time of the second interim analysis (after 40 deaths) in September 1988, 44 centers had recruited 555 patients with a mean duration of follow-up of 271 days. Extrapolation of the mortality rate in the placebo group to 1 year showed a much lower than expected rate: 12% instead of at least 20%. In addition, the proportion of enrolled patients was 12%, contrary to the expected rate of approximately 30%. Analysis of the registry of considered patients predicted that the percentage should have been 49%. The Policy Board recommended the trial be stopped because the study population was not markedly different from those of previous trials. That recommendation was endorsed by the Steering Committee. Enrollment of patients was terminated on December 25, 1987. At that time, there had been twice as many deaths (27) in the placebo group than in the acebutolol group (13).

When the trial was terminated, 607 patients had been recruited by 44 clinical centers (average, 13.8 patients per center; range, 1 to 43); 309 patients received placebo and 298 received acebutolol.

The number of secondary risk factors in both included and excluded patients is given in Table I and the distribution of secondary risk factors in both excluded and ran-

TABLE I Major and Minor Risk Factors (%)

	Excluded ≤48 hours After Admission (n = 719)	Excluded >48 hours After Admission (n = 945)	Included Same Centers (n = 219)	Included Study Total (n = 607)
Minor risk factors				
Age >60 years	68.00	52.00	52.97	61.61
Female	29.40	19.70	22.83	27.18
Prior history				
Angina pectoris	42.10	35.20	41.10	43.99
Unstable angina	27.20	24.10	29.22	29.00
Angina pectoris >5 years	21.70	11.90	14.16	17.96
Nonproven MI	3.80	1.60	2.74	2.47
Acute pulmonary edema	3.70	1.50	1.37	1.65
Severe exertional dyspnea	22.30	12.40	32.42	33.11
Nocturnal dyspnea	3.40	1.60	0.91	1.81
Intermittent claudication	13.80	7.10	8.68	8.90
Valvular disease	3.90	4.40	3.20	5.27
Diabetes mellitus	13.40	10.20	15.53	14.33
Renal failure	4.40	1.30	1.83	3.13
Liver cirrhosis	2.80	0.40	1.83	1.81
Contraindication to oral anticoagulants	—	3.60	4.11	5.60
Present or former smoker	58.50	70.30	72.15	65.07
Hypertension	29.60	20.60	25.11	31.80
Onset of symptoms				
Infarct location other than posterior or inferior	53.90	51.00	63.01	69.36
Shock	6.50	3.30	5.94	6.10
Acute pulmonary edema	13.90	8.20	15.53	14.17
Conduction defect or rhythm disturbance	6.60	8.20	21.00	16.31
Palpitations	3.20	1.90	6.39	9.06
Arrhythmia	7.30	3.90	9.13	12.85
Murmur	19.30	11.80	13.24	14.99
Cyanosis	4.60	1.40	2.28	3.79
Cold hands and feet	9.60	5.00	11.87	10.38
Hepatomegaly	4.60	3.20	4.57	2.97
Hepatojugular reflux	9.00	5.30	10.05	7.58
Early stage				
Breathlessness	27.20	16.80	36.99	41.35
Choking	20.10	12.10	22.83	21.42
Relieved in sitting position	15.20	11.10	20.55	21.91
Smarting	11.10	5.30	5.02	6.26
Foaming expectoration	4.60	2.80	3.20	3.13
Auriculoventricular block	10.70	6.10	10.05	9.23
Heart rate >65 beats/min	76.60	86.50	94.98	93.25
Major risk factors				
Prior history of				
Documented MI	20.30	11.80	22.83	21.58
Dyspnea on flat ground	12.00	4.20	13.24	13.84
Acute stage				
Atrial fibrillation	8.30	5.40	10.50	15.82
Ventricular fibrillation or ventricular tachycardia	3.00	14.60	21.92	26.36
Heart failure	41.50	24.30	48.40	49.59
Early stage				
Sinus tachycardia	—	10.30	26.48	26.85
Recurrent angina pectoris	—	7.00	13.70	15.98
Recurrent MI	—	1.50	3.65	3.62
Number of risk factors (range)	6 (1–25)	5 (0–31)	8 (6–20)	8 (6–20)

TABLE II Significantly Different Baseline Characteristics in the Two Treatment Groups

	Acebutolol		Placebo		
	No.	%	No.	%	p Value
Hypertriglyceridemia	18	6.1	6	1.9	0.009
Atrial fibrillation or flutter*	49	16.6	32	10.5	0.028
Heparin*	294	99.0	297	96.1	0.023
Antihypertensive therapies*	8	2.7	21	6.8	0.018
Pacemaker*	6	2.0	18	5.8	0.016
Asthenia†	143	49.1	167	55.1	0.036
Inotropics†	18	6.2	8	2.6	0.035

* First 48 hours.
† From Day 3 to Day 21.

domized patients is shown in Figure 2. Individual predicted risk was computed from a logistic function constructed from the EPSIM registry data. The distribution of included and excluded patients in relation to their 1-year theoretical risk of mortality is shown in Figure 3. There was no statistically significant difference with respect to predicted risk between the acebutolol group and the placebo group.

The baseline characteristics of the 2 groups were assessed through comparison of 266 baseline variables; only 7 of these 266 characteristics were statistically significantly different ($p < 0.05$) between the 2 groups (Table II). Thus, we can conclude that differences in baseline characteristics were minimal between the 2 groups and that similar patient populations existed in the 2 groups. However, the findings on mortality were adjusted for these 7 variables, among others. Such an adjustment did not substantially change the difference in mortality. The reasons for exclusion of eligible patients are listed in Table III. The most common reasons were contraindications to β-blocking agents or indications for such drugs and inability to participate in the trial.

TABLE III Reasons for Exclusion in 1,664 Patients

	Excluded During First 48 Hours (n = 719)	
Criteria	No.	%
Prior enrollment in APSI	5	0.7
Participation in another study	5	0.7
Inability to enroll	228	32.0
Malignancy	39	5.5
Valvular disease	31	4.4
Age >75 years	97	13.6
Indication for β blockers	128	18.0
Other contraindications to β blockers	131	18.4
Raynaud's syndrome	10	1.4
Chronic bronchopneumopathy	51	7.1
Asthma	20	2.8
Nonproven infarction	57	8.0
Coma	13	1.8
Death	53	7.4
Not available	9	1.3

	Excluded Between Day 3 and Day 21 (n = 945)	
Criteria	No.	%
Complete auriculoventricular block (3rd grade)	8	0.9
Cardiac failure requiring treatment with ≥2 drugs of different classes	103	11.2
Bradycardia (<45 beats/min)	8	0.9
Unstable insulin-dependent diabetes	6	0.7
Sequela of stroke	4	0.4
Indication for coronary bypass surgery	53	5.7
Indication for amiodarone, bepridil, verapamil or diltiazem	98	10.6
Condition preventing study inclusion	124	13.5
Refusal of consent	104	11.6
Risk factors <6	383	41.7
Death	40	4.3
Not available	7	0.7

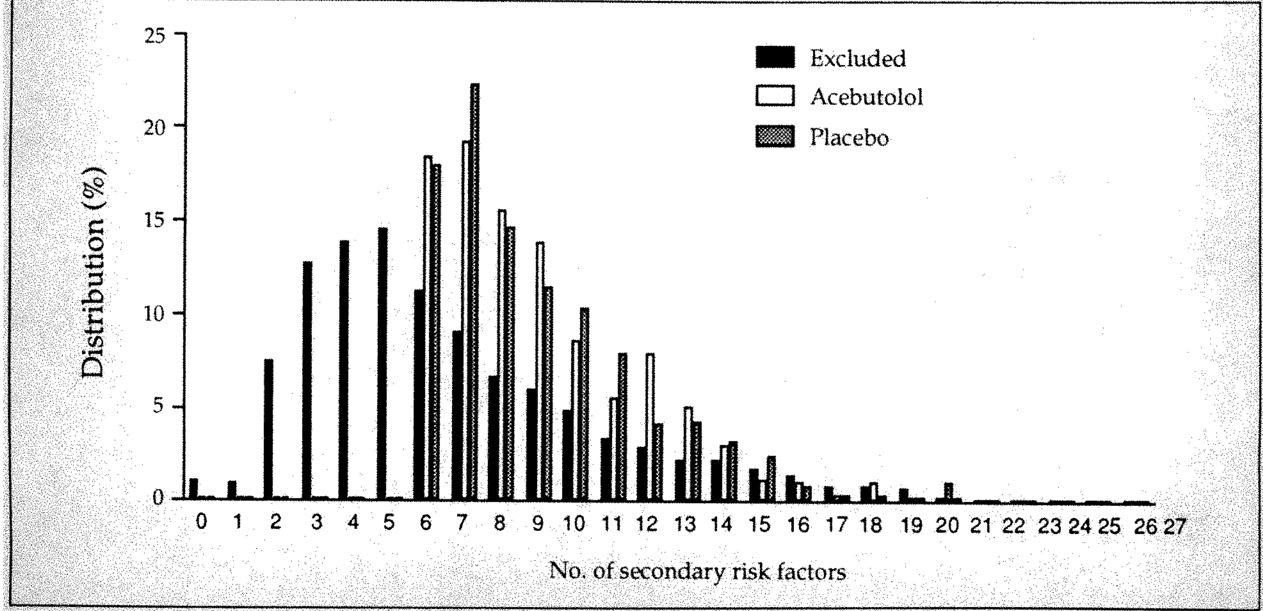

FIGURE 2. Percent distribution of secondary risk factors in excluded and randomized patients.

TABLE IV Expected, Observed, Extrapolated and Theoretical Mortality Rates (%) in Excluded and Randomized Patients

Group	No.	Expected 1-year*	Observed (318 days)	Extrapolated 1-year†	Theoretical 1-year‡
Placebo	309	26.0	11.0	12.4	20.0
Acebutolol	298	—	5.7	6.5	20.0
Excluded§	1465	—	12.3	14.0	14.4
All registered§	1684	17.0	11.8	13.4	15.1

* From analysis of the EPSIM registry (patients still alive at 8 days).
† Exponential extrapolation.
‡ Computed by applying the logistic regression function estimated from the EPSIM registry (patients still alive at 10 days) to APSI patients.
§ Registry kept in 7 centers: patients still alive at 10 days.

TABLE V Observed Risk Reduction According to the Number of Secondary Risk Factors

	Acebutolol		Placebo		
No. of SRF	No.	Risk (%)	No.	Risk (%)	Risk Reduction
6	55	1.82	56	1.78	−0.0182
7	58	3.45	69	5.797	−0.4052
8	46	4.35	45	17.778	−0.7554
9	41	7.32	35	9.375	−0.1463
10	25	4.17	31	9.677	−0.5867
11	16	6.25	24	20.833	−0.7000
12	23	8.7	12	16.667	−0.4783
13	15	13.3	13	23.076	−0.4222
14–20	19	15.79	24	20.83	−0.2421

SRF = secondary risk factors.

The average theoretical 1-year mortality rate for the 309 patients in the placebo group was 20% compared with the expected 1-year mortality rate of 26% from analysis of the EPSIM registry (Table IV). However, the extrapolated 1-year observed mortality rate was 12.4%, a figure lower (although not statistically significant; p = 0.24) than the extrapolated 1-year mortality rate of excluded patients (14.0%) (Table IV).

The withdrawal rates were the same in the placebo and acebutolol groups. In the acebutolol group, a larger number of withdrawals due to a condition that contraindicated treatment with a β-blocker was balanced by a lower number of conditions that made such treatment compulsory.[1]

After an average duration of follow-up of 318 days, only 17 deaths (5.7%) occurred in the acebutolol group, whereas 34 deaths (11%) occurred in the placebo group. Thus, treatment with acebutolol resulted in a 48% reduction in mortality compared with placebo treatment (p = 0.019, 2-tailed; p = 0.013, 1-tailed). The survival curves did not cross-over. The causes of death were validated by an independent panel of experts. There was a marked reduction in vascular deaths in the acebutolol group (12 patients; 4%) compared with the placebo group (30 patients; 9.7%). This 58% reduction in vascular mortality was significant (p = 0.006; 2-tailed). All deaths due to cardiovascular reasons were less frequent in the acebutolol group, including deaths due to heart failure. However, the same number of uncertain causes and noncardiovascular causes of death occurred in both groups.

When the difference in total mortality is adjusted for 15 baseline characteristics that are established prognostic factors (e.g., age and heart rate), the 2-tailed p value is 0.0052. When the difference is adjusted for the secondary risk factors, the 2-tailed p value is between 0.017 and 0.029, depending on the model.

Since overall mortality in the placebo group was less than expected, we addressed the question of the efficacy of acebutolol in high-risk post-MI patients in 3 ways. First, we first split patients in both groups according to

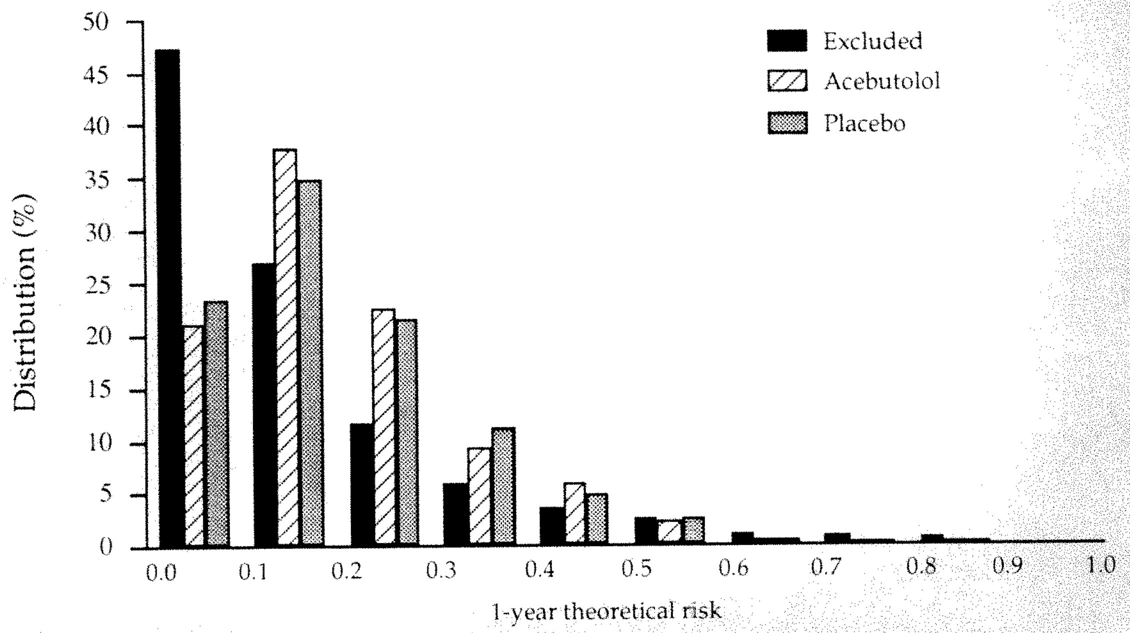

FIGURE 3. Percent distribution of patients and 1-year theoretical mortality risk.

TABLE VI Conditions Possibly Correlated with Poor Prognosis Prior to Randomization

Group	Congestive Heart Failure (no. deaths/no. patients)		Documented MI (no. deaths/no. patients)		Acute Pulmonary Edema (MI) (no. deaths/no. patients)	
	Present	Not Present	Present	Not Present	Present	Not Present
Acebutolol	6/88	11/207	7/62	10/233	1/6	16/289
Placebo	9/77	25/231	12/68	22/241	1/2	33/306
Relative risk	0.58	0.46	0.64	0.47	0.33	0.49
95% CI	0.22–1.57	0.22–0.97	0.27–1.52	0.23–0.97	0.03–3.20	0.26–0.90
p value	0.28	0.02	0.31	0.04	0.35	0.02

CI = confidence interval.

TABLE VII Outcome Correlated with β-Blocking Therapy Prior to Randomization

	Acebutolol (no. deaths/ no. patients)	Placebo (no. deaths/ no. patients)
Received β-blocker therapy[*]	2/49	7/51
Did not receive β-blocker therapy[†]	15/249	27/258

[*] Relative risk 0.30 (0.06–1.36); p = 0.09.
[†] Relative risk 0.58 (0.31–1.06); p = 0.07. Comparison of the 2 subgroups in terms of relative risk was not significant (p = 0.42).

TABLE VIII Outcome Correlated with Nifedipine Therapy During the Trial

	Acebutolol (no. deaths/ no. patients)	Placebo (no. deaths/ no. patients)
Received nifedipine therapy[*]	1/107	3/102
Did not receive nifedipine therapy[†]	16/191	31/207

[*] Relative risk 0.32 (0.03–3.00); p = 0.29.
[†] Relative risk 0.56 (0.32–0.99); p = 0.04. Comparison of the 2 subgroups in terms of relative risk was not significant (p = 0.67).

whether they had <9 or ≥9 secondary risk factors. In the placebo subgroup with <9 risk factors (n = 170), the mortality rate was 7.6%. In the placebo subgroup with ≥9 risk factors (n = 139), the mortality rate was 15.1%. The corresponding mortality rates for the acebutolol subgroups were 3.1% (n = 159) and 8.6% (n = 139), respectively (relative risk of 0.41 and 0.57, respectively; the difference is not significant: p = 0.65). Second, patients were ranked according to their basal risk. Patients with the same number of secondary risk factors were grouped; groups with fewer than approximately 40 patients were grouped together. There were 9 subgroups of patients. The observed mortality rates of the 9 placebo subgroups ranged from 1.8 to 23.1%; in the 9 acebutolol subgroups, mortality rates ranged from 1.8 to 15.8%. There was a positive, significant correlation between the observed mortality in the acebutolol subgroups and the basal risk represented by the observed mortality in the corresponding placebo subgroups (p = 0.026) (Table V). Third, we looked for a possible interaction with baseline characteristics that are correlated with poor prognosis (although such an interaction has not been substantiated in the pooling of 9 previous trials[4]); results are shown in Table VI. Again, there was no indication that efficacy decreased with poor baseline conditions.

Since it has been claimed that withdrawal of β-blocking treatment may be harmful to patients with coronary heart disease, patients were subgrouped according to β-blocking therapy received before randomization.[6,7] A total of 100 patients had received β blockers prior to randomization (Table VII). The relative risk for those patients was 0.30 (0.49 with the Mantel-Haenszel method) with a 95% confidence interval of 0.06 to 1.36 and 0.58 for those without β-blocking treatment (confidence interval, 0.31 to 1.06). The comparison of the 2 subgroups in terms of relative risk was not significantly different (Breslow-Day chi-square = 0.66; p = 0.42). When β-blocking treatment prior to randomization was added as a covariate in the adjustment model, the p values were not substantially changed (p = 0.0067). Hence, there was no evidence that the observed effect of acebutolol on mortality was due to an interaction with withdrawal from prior β-blocking treatment.

Patients were permitted to receive concomitant therapy with nifedipine. A total of 209 patients received nifedipine during the course of the trial. There was no difference in the relative risk for patients who had received nifedipine and those who had not (Breslow-Day chi-square = 0.18; p = 0.67) (Table VIII).

Similar side effects were reported in the placebo and acebutolol groups during the study: dizziness or giddiness, asthenia, headache, insomnia, somnolence, depression, constipation, dyspepsia, nausea, flatulence, rhinitis, shivers, impaired vision, arthralgia, myalgia, rash, and urinary discomfort. Only diarrhea occurred more frequently in the acebutolol group.

Systolic blood pressure was slightly lower in the acebutolol group during the first few follow-up visits (131 vs 136 mm Hg; p = 0.004). This difference decreased during the course of the study and eventually disappeared at 9 months. A similar trend was observed for diastolic blood pressure (79 vs 82 mm Hg; p = 0.006). Average heart rate was significantly lower in the acebutolol group than in the placebo group at 3 months (69.4 vs 78.2 beats/min; p <0.0001); this difference was observed at 12 months (69.1 vs 74.5 beats/min; p = 0.0001). No differences between the 2 groups in clinical examination or functional capacity were reported by the investigators.

The number of rehospitalizations during the study were similar in the acebutolol and placebo groups (33.9 vs 30.1%, respectively), as were the numbers of patients who underwent at least 1 operation (9.1 vs 10.7%, respectively).

DISCUSSION

As discussed elsewhere,[1] this trial was terminated because it did not succeed in selecting patients at high risk. However, patients included in the study did have a higher mean number of secondary risk factors compared with excluded patients (Table I), although patients with a very high number of secondary risk factors were excluded (Fig. 2). When the distributions of theoretical 1-year mortality rates are compared among excluded acebutolol and placebo patients, there is a striking shift of the mode value in randomized patients (Fig. 3). Nevertheless, the APSI data support the hypothesis that acebutolol is more effective in high-risk than in moderately severe patients. First, the extrapolated 1-year mortality rate of the registered target population is 13.4%, not quite different from the extrapolated 1-year mortality rate in the placebo group (12.4%). Furthermore, although the theoretical 1-year mortality rate in the target population is 15.1%, close to the extrapolated rate (13.4%), the theoretical 1-year mortality rate in the placebo group is 20% (Table IV). Second, various approaches for subgrouping patients according to their basal risk show consistently that there was no decreased risk reduction up to a basal observed mortality rate of 23.1% in the placebo patients.

The observed reduction in total mortality (48%) achieved with acebutolol therapy compared with placebo is the greatest observed among the previous 12 trials of β blockers in post-MI patients.[1] A meta-analysis of the 12 published trials with >200 patients who had been started on treatment before discharge confirms that the reduction in 1-year mortality observed in APSI is at least as good as the pooled benefit. This suggests, but does not definitively prove, that acebutolol is more effective than any other β-blocking agent in secondary prevention after MI, despite the fact that the p value for homogeneity is small when APSI is added to the other trials (0.023; the 95% confidence interval for the reduction is 0.27 to 0.90).

It has been claimed that β-blocking agents with intrinsic sympathomimetic activity (ISA) are less effective, if not ineffective, for secondary prevention after MI; data from the 2 trials that evaluated such drugs, the European Infarction Study[8] with oxprenolol and the Australian and Swedish Pindolol Study,[9] gave negative trends. However, no overview of previously published trials has substantiated such a claim, which is now less likely, particularly after our findings with acebutolol, a β-blocking drug with moderate ISA. Nevertheless, the daily dosage of drugs used in APSI might have played a role in our results, since a rather low acebutolol dosage was chosen. Results of a trial conducted by Collett et al[10] indicate that acebutolol appears to be 4 to 7 times less potent on a mass basis than propranolol on exercise tachycardia in healthy volunteers. The daily dose of acebutolol that corresponds to the 320 mg daily dose of propranolol in the β-Blocker Heart Attack Trial[11] is at least 1,380 mg. In the APSI trial, the dose of β-blocking activity was one-third that in the β-Blocker Heart Attack Trial.

CONCLUSION

The results of the APSI trial demonstrate that moderately severe patients following acute MI can benefit from β-blocking treatment. Since acebutolol is a β blocker with mild ISA, this trial refutes the widespread idea that therapy with a β blocker with ISA is not suitable for secondary prevention after acute MI.

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APPENDIX

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Characteristics of Participants at Baseline in the Treatment of Mild Hypertension Study (TOMHS)

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The Treatment of Mild Hypertension Study (TOMHS) is a randomized, double-blind clinical trial currently being conducted to compare the effects of nonpharmacologic therapy alone with those of 1 of 5 active drug regimens combined with nonpharmacologic therapy, for long-term management of patients with mild hypertension. Six classes of drugs were studied: (1) acebutolol (β blocker), (2) amlodipine (calcium antagonist), (3) chlorthalidone (diuretic), (4) doxazosin (α_1 antagonist), (5) enalapril (angiotensin-converting enzyme inhibitor) and (6) placebo. All participants received nutritional-hygienic advice to reduce weight and sodium and alcohol intakes and to increase physical activity. End points include blood pressure change, side effects and quality-of-life indices; incidence of electrocardiographic and echocardiographic abnormalities; and incidence of cardiovascular clinical events, including death, among participants receiving drugs as first-step treatment as well as nonpharmacologic treatment compared with incidence among those participants randomized to nonpharmacologic treatment only as the initial step.

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Mild hypertension, defined as diastolic blood pressure between 90 and 104 mm Hg, is the most common form of hypertension in the United States and accounts for the majority of excess coronary artery disease (CAD) deaths attributable to hypertension.[1] Approximately 40 million Americans have mild hypertension, of whom half are being treated pharmacologically. Epidemiologic data have shown that treatment of mild hypertension prevents stroke; an approximately 40% reduction in stroke events has been achieved.[2,3] However, the reduction in CAD events has not been as great as expected from observational studies. Meta-analysis of a number of mild hypertension treatment trials has revealed a 14% reduction in CAD, versus a predicted reduction of about 20 to 25%.[3]

The less-than-expected benefit of CAD prevention in treating mild hypertension has raised several questions. Is there a danger in lowering blood pressure too much? Do the biochemical changes often caused by diuretics (low serum potassium, increased uric acid, increased lipids) pose a greater risk than does mild hypertension left untreated? Should nonpharmacologic therapy play a larger role? If so, who should rely on nonpharmacologic therapy, and for how long?[4] Since data from long-term intervention trials showed reduced morbidity and mortality with use of either diuretics or β blockers, what role do other classes of antihypertensive agents, such as α blockers, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers, play in preventing morbidity and mortality independent of blood pressure change? Specifically, at what stage in the therapeutic armamentarium should these agents be introduced? The Treatment of Mild Hypertension Study (TOMHS) was designed to answer some of these questions.

PATIENTS AND METHODS

Study design: TOMHS is a randomized, double-blind clinical trial currently being conducted in 4 centers in the United States. All participants in the trial receive nutritional-hygienic advice aimed at reducing weight with a low-fat diet, lowered dietary sodium and alcohol intakes and increased leisure-time physical activity. In addition, participants are randomized to receive 1 of 5 antihypertensive drugs or placebo. Specific aims are to compare (1) blood pressure lowering, side effects and quality-of-life indices among men and women with mild hypertension receiving nutritional-hygienic treatment plus 1 of 5 active drug treatments or placebo; (2) the incidence of electrocardiographic and echocardiographic abnormalities

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among participants receiving these 6 different treatments for mild hypertension; and (3) the incidence of cardiovascular clinical events, including death, among participants receiving drugs as the first-step treatment as well as nonpharmacologic treatment with incidence in those patients randomized to nonpharmacologic treatment only as the initial step. It is planned to follow all participants for a minimum of 4 years after randomization.

Study patients: Men and women between the ages of 45 and 69 years, not taking antihypertensive medication at the first of 3 eligibility visits prior to randomization, were included if diastolic blood pressure was 90 to 99 mm Hg at the first 2 eligibility visits and averaged 90 to 99 mm Hg over 3 eligibility visits.[1] Participants already taking antihypertensive drugs at the first eligibility visit were potentially eligible if they were prescribed only 1 type of agent and if, after drug withdrawal, their diastolic blood pressure averaged 85 to 99 mm Hg at 3 eligibility visits. Participants with evidence of cardiovascular disease or life-threatening illness or who were unable to make nutritional changes were excluded.

Randomization was to 1 of 6 groups, all receiving nutritional-hygienic treatment: (1) acebutolol, a β_1-cardioselective blocker with intrinsic sympathomimetic activity (400 mg/day); (2) amlodipine, a calcium antagonist (5 mg/day); (3) chlorthalidone, a diuretic (15 mg/day); (4) doxazosin, an α_1 antagonist (2 mg/day following 1 mg/day for 1 month); (5) enalapril, an ACE inhibitor (5 mg/day); and (6) placebo. Randomization occurred at the end of the third eligibility visit after completion of written informed consent for eligible participants.

Measurements: Blood pressure was measured with a Hawksley random-0 sphygmomanometer on the right arm with the participant seated. Prior to blood pressure measurement, the participant rested for 5 minutes, and pulse and room temperature were recorded. Blood pressure observers were trained, certified and monitored using previously described methods.[5]

Sodium intake was monitored based on 2 consecutive overnight urine collections (adjusted to 8 hours) every 6 months. Urine was analyzed for potassium and creatinine, as well as sodium. Sodium intake was also assessed based on food records. Records were edited at each of the 4 clinical centers by a trained nutritionist and then sent to the University of Minnesota Nutrition Coordinating Center for coding, entry and nutrient analysis.[6]

Participants were weighed without shoes on balanced scales, collaborated on a weekly basis with use of a standard 50-pound weight. Baseline weight was the average of measurements taken at the second and third eligibility visits. Physical activity was assessed from daily diaries. Participants recorded type, frequency and duration of activity. This information was then converted into "physical activity points." Each point was calculated to be comparable to 4 kilocalories of energy expenditure.

Blood chemistries, including fasting blood lipids, were determined prior to randomization; repeat analyses are being done at regular intervals during follow-up.[1] Plasma total cholesterol, high-density lipoprotein cholesterol and triglycerides were measured directly. Very low-density

TABLE I Selected Baseline Characteristics of 902 TOHMS Randomized Participants

Baseline Characteristics	Mean	Standard Deviation
Not prescribed antihypertensive medication at entry (%)	39.1	—
Age (years)	54.8	6.4
Gender (% male)	61.8	—
Race (% black)	19.6	—
Weight (lbs)	187.4	31.1
Body mass index (kg/m^2)	28.9	3.6
Overnight urinary sodium excretion (mEq/8 h)	53.6	27.9
Alcohol use (%)	72.7	—
Drinks/wk for alcohol drinkers	5.0	4.9
Plasma cholesterol (mg/dl)	228.3	38.4
Cigarette smokers (%)	10.9	—

TABLE II Average Level of Systolic and Diastolic Blood Pressures at Each Eligibility Visit According to Use of Antihypertensive Medication at the Initial Eligibility Visit

	Not Taking Antihypertensive Medication at Visits 1 to 3 (n = 353)		Taking Antihypertensive Medication at Visit 1 (n = 549)		Total (n = 902)	
	Mean	SD	Mean	SD	Mean	SD
Systolic blood pressure (mm Hg)						
Visit 1	146.6	13.9	132.3*	13.9	137.9	15.6
Visit 2	143.0	13.8	140.6†	13.7	141.5	13.8
Visit 3	139.8	13.1	138.8†	14.1	139.2	13.7
Average visits 2 and 3	141.4	12.2	139.7†	12.6	140.4	12.4
Diastolic blood pressure (mm Hg)						
Visit 1	94.2	2.8	84.2*	6.6	83.1	7.3
Visit 2	93.2	2.5	90.3†	3.9	91.4	3.7
Visit 3	91.0	4.1	88.8†	5.0	89.7	4.8
Average visits 2 and 3	92.1	2.6	89.6†	3.5	90.5	3.4

* Participant taking antihypertensive medication.
† Participant not taking antihypertensive medication.

TABLE III Selected Baseline Characteristics of Randomized TOMHS Participants According to Use of Antihypertensive Medication at the Initial Visit

	Not Taking Antihypertensive Medication (n = 353)		Taking Antihypertensive Medication (n = 549)	
Baseline Characteristics	Mean	SD	Mean	SD
Age (years)	54.3	6.4	55.1	6.4
Gender (% male)	66.0		59.0	—
Race (% black)	21.2	—	18.6	—
Body mass index (kg/m^2)	28.7	3.5	29.0	3.6
Overnight urinary sodium excretion (mEq/8 h)	53.1	25.8	54.0	29.3
Alcohol use (%)	70.9	—	73.8	—
Drinks/wk for alcohol drinkers	5.4	5.2	4.7	4.8
Plasma cholesterol (mg/dl)	230.7	38.3	226.7	38.4
Cigarette smokers (%)	13.7	—	9.1	—

TABLE IV Selected Baseline Characteristics of TOMHS Randomized Participants by Race and Gender

Baseline Characteristics	White Women (n = 233)	Black Women (n = 112)	White Men (n = 492)	Black Men (n = 65)
Age (years)	55.0	53.7	55.0	54.0
Weight (lbs)	163.2	175.6	200.3	296.2
Body mass index (kg/m^2)	28.1	29.8	29.1	28.3
Overnight urinary sodium excretion (mEq/8 h)	43.9	52.8	57.8	57.9
Alcohol use (%)	72.3	58.2	77.2	64.1
Drinks/wk for alcohol drinkers	3.6	3.0	5.7	6.8
Plasma cholesterol (mg/dl)	234.9	231.5	224.3	228.5
Cigarette smokers (%)	8.6	20.5	7.0	32.3
Antihypertensive treatment at initial visit (%)	66.1	63.4	59.6	47.7
Systolic blood pressure (mm Hg)	141.7	141.2	140.1	136.4
Diastolic blood pressure (mm Hg)	90.0	90.5	90.8	90.6

lipoprotein cholesterol was approximated as triglycerides divided by 5, and low-density lipoprotein cholesterol was then determined by subtraction.[7]

Resting and 24-hour ambulatory electrocardiograms and echocardiograms were also obtained prior to randomization and are being recorded annually.

Data analysis: Analysis of variance and covariance was used to summarize baseline differences among randomized participants according to race-gender and to antihypertensive medication status at the initial eligibility visit. The chi-square test was used for comparisons of categorial variables.[8] As a result of randomization, participants in the 6 treatment groups were similar at baseline.

RESULTS

Recruitment of participants: The 4 participating clinical centers screened 11,914 men and women for entry into the study. Of these, 6,703 were taking antihypertensive medication at the initial eligibility visit and 5,211 were prescribed medication. A total of 902 participants were eventually randomized.

Characteristics of all randomized participants: Table 1 summarizes selected characteristics of randomized participants. Of the 902 randomized participants, 353 (39%) were not taking antihypertensive medication at the first eligibility visit. The average age was 55 years, and 62% of participants were men and 20% were black. Most participants were overweight (mean body mass index = 28.9 kg/m^2), had high-average sodium excretion (mean 53.6 mEq/8 h), and were moderate alcohol drinkers. Total plasma cholesterol level averaged 228 mg/dl; 11% of participants reported smoking cigarettes.

Table 2 summarizes systolic and diastolic blood pressure levels for randomized participants according to use of antihypertensive medication at the initial eligibility visit. As a result of the blood pressure eligibility criteria employed, randomized participants had "mildly" elevated blood pressure on 3 occasions. Blood pressure level for participants not taking antihypertensive medication at the initial visit averaged 141.4/92.1 mm Hg over the last 2 eligibility visits. Among participants taking antihypertensive medication at the initial visit, blood pressure increased (by approximately 7 mm Hg for systolic and 5 mm Hg for diastolic) following withdrawal of drugs. Blood pressure at visits 2 and 3 averaged 139.7/89.6 mm Hg. For both stratum combined, baseline systolic and diastolic blood pressures averaged 140.4 and 90.5 mm Hg, respectively.

Table 3 summarizes other baseline characteristics for participants according to their use of antihypertensive medication at the initial eligibility visit. Except for gender, demographic and other characteristics were similar for these 2 groups of participants. Of participants not taking antihypertensive medication at the initial eligibility visit, 66% were men compared with 59% among participants taking medication.

Table 4 characterizes randomized participants according to race and gender. Average age was similar for these 4 groups. Black women were significantly heavier (175.6 pounds) than white women (163.2 pounds), but black and white men had similar weights and body mass index. Urinary sodium excretion was significantly lower among white women (43.9 mEq/8 h) compared with the other 3 race-gender groups. White participants reported more alcohol consumption than blacks; among reported drinkers, men reported drinking more than women (approximately 6 drinks/week compared with 3 drinks/week).

Cholesterol and smoking levels also varied according to race and gender. White men had significantly lower plasma cholesterol levels (224 mg/dl) compared with other race-gender groups (233 mg/dl for average of other groups). More blacks than whites reported smoking cigarettes (20.5% versus 8.6% for women and 32.3% versus 7.0% for men).

As noted previously, more women than men were taking antihypertensive drugs at the initial eligibility visit; this was true for both blacks and whites. More whites than blacks were prescribed antihypertensive drugs. Diastolic blood pressure levels at baseline were similar for the 4 race-gender groups; however, baseline systolic blood pressure was lower for black men (136 mm Hg) than for other race-gender groups (average, 141 mm Hg).

DISCUSSION

In 1988, the Joint National Committee recommended expansion of the number of antihypertensive drugs for initial use in stepped-care treatment. The 1988 Joint National Committee also recommended nonpharmacologic treatment prior to pharmacologic treatment for patients with diastolic blood pressure between 85 and 99 mm Hg and as an adjunct to drug treatment for those with higher levels of diastolic blood pressure.[9]

TOMHS is the first major randomized clinical trial to evaluate a multifactor nutritional approach (weight, sodium and alcohol intakes) as the initial step for treating mild hypertension. It is also the first clinical trial to compare simultaneously 5 classes of antihypertensive drugs (4 of which are recommended by the Joint National Committee). Each drug is given in low doses and with concurrent nutritional-hygienic advice. The focus of TOMHS is on mild hypertension because (1) tens of millions of persons are affected[1]; (2) such persons are at increased risk of CAD, as recently underscored by the long-term follow-up of the 361,662 men screened in the Multiple Risk Factor Intervention Trial[10] and a recent meta-analysis of observational studies[2]; and (3) the optimal treatment approach is unclear, since reductions in CAD mortality rates in clinical trials have been less than expected based on the observational data.[3]

According to the 1988 Joint National Committee guidelines, all of the 353 participants who were not taking antihypertensive medications at the initial eligibility visit qualify for nonpharmacologic therapy, and 89% of them also qualify for initial drug treatment (20% of patients had diastolic blood pressure ≥95 mm Hg and 69% had an average diastolic blood pressure in the range of 90 to 94 mm Hg, as well as other risk factors, such as plasma cholesterol level ≥240 mg/dl, history of cigarette smoking, male gender, or all 3). The 549 participants taking antihypertensive medication at the initial eligibility visit previously had been determined by their usual source of medical care to require treatment. The median duration of treatment at baseline for these participants was 5 years. Thus, the participants enrolled in TOMHS have characteristics that are particularly relevant to the guidelines of the Joint National Committee.

All participants in TOMHS have now been followed for at least 2 years. Initial analyses have focused on blood pressure, side effects and quality-of-life differences among the treatment groups. Analyses comparing incidence of echocardiographic and electrocardiographic abnormalities are in progress. With the 2 additional years of follow-up planned, there will be increased power for the comparison of all active drug groups combined with the placebo group (nutritional-hygienic treatment alone) for cardiovascular clinical events. These, along with certain subgroup comparisons, such as black versus whites for blood pressure control using different treatments, will provide a more valid basis for future treatment guidelines.

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Arterial Protection: A Neglected but Crucial Therapeutic Goal

Norman M. Kaplan, MD

Hypertension is accompanied by 2 major types of arterial pathologic conditions: smooth muscle hypertrophy of arteriolar resistance vessels and atherosclerosis, primarily involving the larger arteries. Smooth muscle hypertrophy may develop either as a secondary defense against elevated intravascular pressure or as a primary defect responsible for the increased pressure. Insulin and a number of other trophic stimuli may play a pathogenetic role in vascular hypertrophy. Reducing blood pressure and trophic stimuli may cause hypertrophy to be reversed. Because atherosclerosis may be markedly accelerated by hypertension, especially in the presence of concomitant risk factors, such as hypercholesterolemia, cigarette smoking and diabetes mellitus, antihypertensive treatment may attenuate or even reverse the extent of atherosclerosis, but only when the causative factors are also corrected. Some commonly used antihypertensive agents, e.g., diuretics and β blockers without intrinsic sympathomimetic activity, often aggravate hypercholesterolemia and glucose intolerance, thereby diminishing their potential protective value. Other types of drug therapy, such as α blockers, β blockers with intrinsic sympathomimetic activity or other vasodilator activity, angiotensin-converting enzyme inhibitors and calcium entry blockers that may not induce biochemical changes, should provide better control of multiple risks and thereby better protection against atherosclerosis. With a better understanding of how hypertension induces arterial damage, clinicians will be able to provide more appropriate treatment and, it is hoped, alleviate such damage.

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In hypertension trials, the major end points of cardiovascular protection have been coronary events and strokes.[1–4] Specifically, these trials were designed to assess the value of various types of antihypertensive therapies in reducing the incidence of myocardial infarction and stroke, or both. Because of this focus, little, if any, effort was made to evaluate arterial changes or the effects of antihypertensive drugs on the arterial wall. Only major target organ damage that results from arterial damage was quantified, in part because it was easy to recognize.

Traditionally, the arteries have been viewed as simple, passive conduits of blood to the tissues, but clinicians today recognize that the arteries are complex, active participants in cardiovascular function. Both the endothelium and the vascular smooth muscle cells produce and secrete various autocrine substances (i.e., acting within the cell of origin) and paracrine substances (i.e., acting within adjacent cells). These substances have profound effects on arterial function and structure.[5,6] In addition, these cells respond to and likely secrete endocrine signals that spread their influence and reactivity further.

This article reviews some of the recent findings regarding endothelial and smooth muscle cell functions and how they may be altered in hypertension. An analysis of the structural changes that are seen in hypertension will follow, with a reminder that it is not yet known whether all of the structural changes are secondary to functional alterations, or whether they represent primary alterations that lead to hypertension. Last, the small amount of direct evidence available regarding the effects of various antihypertensive agents on the arteries will be reviewed.

ENDOTHELIAL CELL

The vascular endothelium, which envelops the circulating blood in a continuous monolayer, performs various functions to maintain the fluidity of the blood and the patency of the blood vessels.[7] These functions involve interactions with circulating vasoactive substances, including angiotensin, bradykinin, acetylcholine, adenosine and thrombin (Fig. 1). In addition, the endothelium synthesizes a large number of active substances including interleukin-1, tissue plasminogen activator, various growth-promoting factors and vasoactive factors including prostacyclin, endothelium-derived relaxing factors (EDRF) and at least 2 endothelium-derived constricting factors. One of these, endothelin, has recently been identified and characterized.[8] Many of the circulating substances may mediate their vasoactivity through EDRF (Fig. 1). One of these evanescent relaxing factors appears to be nitric oxide, the same substance that is released

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TABLE I Effects of Hypertension on Morphology of Endothelium

- Increased permeability to high molecular weight substances
- Increased permeability to mitogenic and vasoactive blood-borne substances
- Increased endothelial cell size and volume
- Increase in the number of homocellular tight junctions
- Disruption of gap junction morphology
- Accelerated rate of replication of endothelium during the initial phase

Adapted from *Am J Cardiol.*[11]

TABLE II Paracrine and Autocrine Influences on Vascular Reactivity

- Endothelium
  - Prostanoids
  - Angiotensin
  - Endothelium-dependent relaxing factor
  - Endothelium-dependent constricting factor
  - Bradykinin
  - Thrombin
- Smooth muscle cell
  - Prostanoids
  - Angiotensin
  - Platelet-derived growth factor
- Nerve endings
  - Norepinephrine
  - Neuropeptides
- Blood cells
  - Serotonin
  - Thromboxane

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TABLE III Autocrine and Paracrine Influences on Blood Vessels

- Vasoactive agents
  - Angiotensin
  - Serotonin
  - Bradykinin
  - Prostaglandins
  - Vasopressin
  - Norepinephrine
  - Insulin
- Growth-regulating factors
  - Autocrine
  - PDGF
  - IGF-1
  - Heparin
- Paracrine
  - PDGF
  - Monocyte-derived growth factor
  - Endothelium-derived growth factor
  - Heparin
  - IGF-1
  - TGF-β
  - Epidermal growth factor
  - Prostaglandins
- Oncogenes

IGF-1 = insulin-like growth factor; PDGF = platelet-derived growth factor; TGF-β = β-transforming growth factor.
Adapted from *Am J Cardiol.*[6]

from vasodilator nitrate drugs such as nitroprusside and glyceryl trinitrate.[9] As has been recently summarized,[10] EDRF and endothelin may modulate and stabilize vasomotor tone while preserving flexibility in its dynamic control.

A number of morphologic changes within the endothelium occur after the induction of hypertension (Table I).[11] These changes can activate a variety of autocrine and paracrine influences, both on vascular reactivity (Table II) and on the growth of the media of the blood vessel (Table III). Many of these changes are associated with both hypertension and atherosclerosis.[12]

SMOOTH MUSCLE CELL

The persistence of hypertension, in whatever manner it arises, is related to medial thickening. This is induced by both hypertrophy and hyperplasia of the smooth muscle cells within the media.[12] In keeping with the concept first proposed by Folkow,[13] various stimuli, which initially increase pressure, produce small structural alterations in the resistance vessels. These structural alterations are amplified and accentuated by an increasingly large number of substances that act to cause smooth muscle cell growth (Table III). Obviously, the roles of the multiple trophic influences vary according to the form and stage of hypertension. The role played by each and the manner by which they are mediated remain unknown but are the object of a great deal of current research.

EFFECTS OF ANTIHYPERTENSIVE AGENTS

Little is known about the effect of blood pressure reduction on the various functional and structural changes in the arteries. Even less is known about the roles of individual antihypertensive agents, in part because none of the large-scale trials of antihypertensive therapy has evaluated the overall effects of antihypertensive agents on peripheral arterial disease. Experimental models of hypertension have usually shown that reduction of blood pressure prevents the development of or regresses the extent of structural thickening that is seen in untreated hypertension.[14] This has been shown with β blockers, the angiotensin-converting enzyme inhibitor captopril and the calcium channel blocker verapamil. However, reversal of hypertrophy has not been observed with hydralazine, perhaps due to reflex increase in sympathetic nervous activity.

In humans, traditional hemodynamic measurements of cardiac output and peripheral resistance[15] as well as measurements of hand blood flow resistance at maximal vasodilation[16] have been obtained to assess the effects of antihypertensive therapy on vascular structure. In 1 study, Jennings et al[15] reported that near-normal hemodynamics were restored after 1 year of antihypertensive therapy. In another study, Sivertsson and colleagues[16] concluded that hypertensive vascular changes seem to be partly, but not completely, reversible after 5 years of blood pressure–lowering therapy.

FUTURE NEEDS

Because of the many shared features of the pathophysiology of hypertension and atherosclerosis, it seems essential to consider a reduction in all of the risk factors for the latter when treatment is directed toward the former. Atherosclerosis is markedly accelerated by hypertension, even more so in the presence of concomitant risk

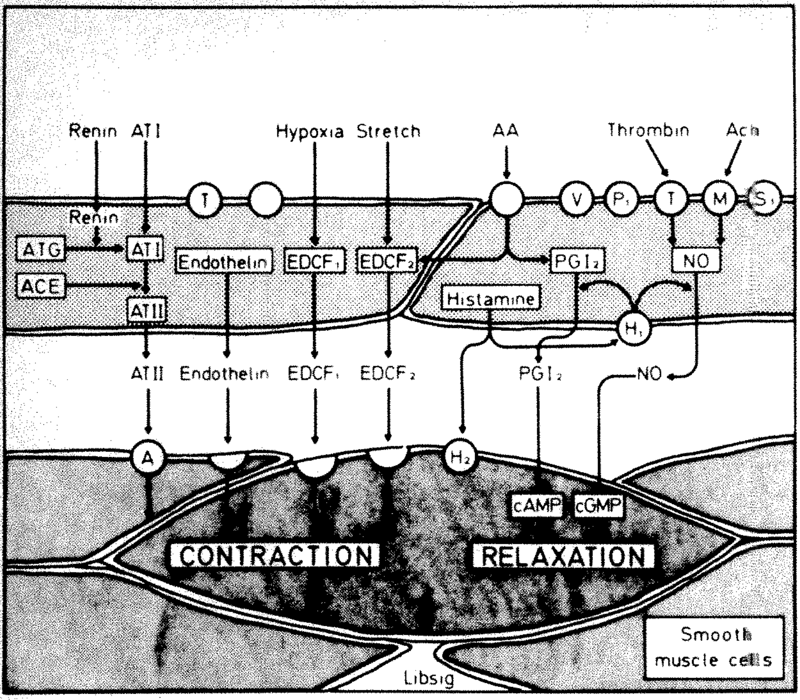

FIGURE 1. Endothelium-derived vasoactive substances. AA = arachidonic acid; ACE = angiotensin-converting enzyme; ATG = angiotensinogen; ACh = acetylcholine; AT I = angiotensin I; AT II = angiotensin II; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; EDCF = endothelium-derived constricting factor(s); H = histamine; M = muscarinic receptor; NO = nitric oxide; P = purinergic receptor; PGI_2 = prostacyclin; S = serotonergic receptor; T = thrombin receptor; V = vasopressin receptor. (Reproduced with permission from *J Cardiovasc Pharmacol*.[7])

factors such as hypercholesterolemia, cigarette smoking, diabetes and upper body obesity. The therapy of hypertension may attenuate or even reverse the extent of atherosclerosis, but only if it is accompanied by correction and inhibition of the other causative factors.

In the past, some commonly used antihypertensive medications, such as diuretics and β blockers without intrinsic sympathomimetic activity often aggravated hypercholesterolemia and glucose intolerance, thereby diminishing their potential value. Today, the use of other antihypertensive agents that may not induce biochemical changes should provide better control of multiple risks and thereby better protection against atherosclerosis. These include the use of β blockers with intrinsic sympathomimetic activity, such as acebutolol, α blockers, angiotensin-converting enzyme inhibitors and calcium entry blockers.[17]

CONCLUSION

Recent concerns about the safety of specific antihypertensive agents has led to increased interest in antihypertensive treatment that may prevent coronary and cardiovascular disease. With a better understanding of how hypertension induces arterial damage, it is hoped that clinicians will be able to provide more appropriate treatment of hypertension and alleviate such damage.

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Mechanical Factors in Large Artery Disease and Antihypertensive Drugs

Jaime Levenson, MD, Isabelle Pithois-Merli, MD, and Alain Simon, MD

Hypertension may induce early alterations in large arteries by 2 mechanical stresses: one related to intravascular pressure, the other to blood flow dynamics. Distending pressure force acts in a circumferential direction, inducing decreased arterial distensibility. Arterial distensibility can be evaluated in humans by measurement of arterial compliance and pulse-wave velocity. It is well established that in chronic hypertension age and elevated pressure act together to increase arterial rigidity. Blood flow dynamics induce frictional forces in the endothelial surfaces of arteries. These forces, expressed by shear stress, are proportional to the viscosity of the blood and to the velocity gradient at the arterial wall. Measurement of blood viscosity and evaluation of velocity profile in the brachial arteries of hypertensive subjects have shown a reduction in wall shear rate and stress despite the elevation in blood viscosity. Several studies have shown that drug therapy that successfully reduces blood pressure does not necessarily improve arterial compliance. In contrast, few data are available on the effects of antihypertensive medication on arterial wall shear in humans. Arterial compliance and wall shear stress are 2 main therapeutic targets of potential importance in the physiopharmacologic approach to the effects of hypertension on atherogenesis.

(Am J Cardiol 1990;66:39C–42C)

Hypertension may induce early alterations in large arteries by 2 mechanical stresses: one related to intravascular pressure, the other to blood flow dynamics. Distending pressure force acts in a circumferential direction, inducing decreased arterial distensibility, which can be evaluated in humans by measurement of arterial compliance and pulse-wave velocity.[1] Blood flow dynamics induce frictional forces in the endothelial surfaces of arteries.[2] The forces, expressed by shear stress, are proportional to the viscosity of blood and to the velocity gradient at the wall. Measurement of blood viscosity and evaluation of velocity profile in the brachial arteries of subjects with hypertension have shown a reduction in wall shear rate and stress despite the elevation in blood viscosity.[3,4] Such abnormalities merit attention because of the potential role of low shear in cholesterol transport[5] and genesis of atherosclerotic plaque.[6] This article summarizes some of the attempts to evaluate arterial compliance and shear stress in the physiopharmacologic approach to the effects of hypertension on blood vessels in humans.

MECHANICAL STRESS RELATED TO INTRAVASCULAR PRESSURE

Intraluminal pressure is the result of both compressing and distending forces, which act in opposition to generate arterial wall tension. In general, compressing forces decrease the radius of a vessel, while distending forces tend to increase the circumference of a vessel. The primary effect of distending pressure on arteries is the modification of arterial caliber, which increases when blood pressure increases as a consequence of the distensibility of the arterial walls. This phenomenon partly explains the increase in diameter of a large artery such as the brachial artery observed in patients with hypertension.[1] Since the circumferential tension is proportional to the product of arterial diameter and arterial pressure, the increase in arterial diameter resulting from elevated blood pressure acts in concurrence with the increase in arterial pressure and multiplies the effect of blood pressure on arterial wall tension. Furthermore, the complex effect of distending pressure on the diameter of arteries is nonlinear, because it is governed by the biphasic elastic composition of arterial walls.[7] At low and normal pressure ranges, only elastin is stretched, resulting in high distensibility of the arterial wall, while at higher pressures, collagen fibers are drawn taught, and distensibility decreases logarithmically as the effective rigidity increases.[8] The first obligatory mechanism that contributes to high arterial rigidity in the hypertensive state is the blood pressure elevation that, per

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se, stretches arterial walls, thereby stiffening the arteries. This occurs because of the biphasic organization of the arterial walls into bioelastomers.[8]

In chronic hemodynamic conditions, the mechanical effect of blood pressure elevation is influenced both by age and arterial atheroma. Aging and, similarly, blood pressure elevation increase arterial stiffness by increasing the collagen to elastin ratio inside the arterial walls.[9] Other factors may decrease arterial compliance in the hypertensive state, such as functional influences on neurohormonal factors that act on arterial smooth muscle, structural alteration of the arterial walls, or both.[1,10-12] Whatever its mechanisms, high arterial rigidity that occurs during hypertension impairs the buffering function of the arterial tree to the pulsatility of the heart and accordingly increases pressure pulsatility.[13] Increased pulsatility of cyclic arterial wall stress may represent a major cause of fatigue of arterial bioelastomers.

MECHANICAL STRESS RELATED TO BLOOD FLOW DYNAMICS

Wall shear stress represents the frictional force applied by the circulating blood column on the intimal surface of arteries. This force is transmitted to the endothelium and tends to displace the endothelial cells in the direction of blood flow. Wall shear is the product of blood viscosity and the velocity gradient at the wall. Elevated blood viscosity in the hypertensive state is inversely related to shear rate.[12] In addition, the degree of elevation of blood viscosity can be correlated with both systolic and diastolic blood pressure levels. Both the hematocrit level and the fibrinogen concentration contribute to the observed increased blood viscosity.[12-14] Wall shear rate, or the velocity gradient at the endothelium, represents the ratio between the blood velocity in the vicinity of the endothelium and its distance from the endothelium. This ratio is also the slope of the velocity profile at the arterial wall.[2] In Poiseuille conditions of flow, which can be applied to the mean component of pulsatile flow and maximum pulsatile flow (peak systolic flow),[2] the velocity profile in a straight large artery (e.g., the brachial artery) is parabolic and determined by 2 primary measurements: arterial diameter and blood velocity in the center line of the artery.[3]

A complex model such as the Womersley model has been used to study the effect of the oscillating shear phenomenon on the endothelium surface.[4] With use of pulsed Doppler velocimeter with a micrometric probe displacement providing instantaneous real-time velocity profiles, it was shown that in the brachial artery, steady and oscillating shear rates were lower in patients with hypertension than in normotensive subjects.[3,4] In addition, despite higher blood viscosity, wall shear stress decreased in the brachial artery of patients with hypertension as a consequence of the marked reduction in wall shear rate.[3,4] The low shear conditions observed in the brachial artery, taken as an in vivo model of a peripheral large artery, might modify the residence time and rate of transport of macromolecules across the arterial wall,[5] and the functional or structural status of the endothelial cell, or both, thus contributing to the atherogenic process in arteries.[6] However, further investigation evaluating wall shear conditions during the cardiac cycle and at various sites on the arterial tree, particularly those exposed to a high risk of atherosclerotic lesions, is required for a more complete assessment of the influence of hypertension on the endothelium-blood interface.

MECHANICAL FACTORS AND ANTIHYPERTENSIVE MEDICATION

Arterial compliance: The effects of antihypertensive drugs on the distensible properties of large arteries in humans with hypertension vary greatly from drug to drug and are unrelated to the magnitude of blood pressure reduction.[15] Improved arterial compliance was reported after the chronic administration of acebutolol, isosorbide dinitrate, captopril, nicardipine and nitrendipine at doses that caused similar reductions in blood pressure. In contrast, urapidil, hydralazine and cadralazine did not affect arterial compliance, which remained below normal values.[15] This short-term drug-induced modification in the elastic properties of large arteries also has been observed during long-term therapy. Acebutolol,[16] carteolol,[17] enalapril[18] and nicardipine[19] have been reported to improve forearm arterial compliance during long-term therapy, whereas atenolol,[17] clonidine[20] and propranolol[18] have not.

Wall shear stress: Few data are available on the effect of antihypertensive medication on the wall shear phenomenon in humans. A recent 3-month, double-blind study[21] was designed to test the in vivo participation of shear stress in the brachial circulation of patients with hypertension. Two β-blocking drugs, atenolol, a selective β-adrenergic agonist, and carteolol, a nonselective β-adrenergic antagonist, were reported to have opposite effects on these parameters. During exclusion of the hand when the brachial circulation is predominantly a voluntary, muscular circulatory bed, atenolol significantly decreased blood velocity and blood flow and increased vascular resistance, whereas carteolol tended to increase blood velocity and flow and significantly decreased vascular resistance.[17] Blood velocity and flow were higher and vascular resistance lower with carteolol than with atenolol, indicating a relative vasodilation of the forearm small arteries with carteolol, compared with atenolol.[17] Moreover, shear rate and stress were significantly higher after carteolol than after atenolol, although both were associated with similar changes in blood viscosity.[21] The differences between the 2 β-blocking drugs may modify the physiological response of endothelial cells to flow, constituting one of the endothelium-mediated mechanisms that may explain the different vasoactive responses of the 2 drugs.

Similar rheologic benefits have been observed with acebutolol. Ten previously untreated ambulatory hypertensive patients received acebutolol therapy for 3 months at an average daily dose of 489 ± 59 mg after a 1-month placebo period. Compared with the placebo baseline period, acebutolol significantly decreased systolic and diastolic blood pressure ($p < 0.01$), perhaps due to arteriolar dilatation as indicated by the decrease in forearm vascular resistance ($p < 0.05$). Large artery distensibility was improved, as shown by the decrease in the brachial to radial pulse-wave velocity (strain gauge mechanography[10]) and the increase in forearm arterial compliance (pulsed Doppler[15]) observed after acebutolol therapy. Acebutolol did not induce any change in blood viscosity at a shear rate of 96 s^{-1} (coaxial cylinder viscosimeter[12]). Wall shear rate and stress increased, but this was insignificant. A positive correlation between pulse-wave velocity and shear rate and stress was observed both before and after acebutolol treatment (Fig. 1), suggesting that shearing forces transmitted to the endothelial cells may participate in changes in vascular tone of the large arteries. This is in agreement with evidence that suggests that shear stress may modulate the release of endothelium-derived relaxing factors or down-regulate the preproendothelin gene.[22]

CONCLUSION

Arterial compliance, as an assessment of the elastic properties of large arteries, and wall shear stress, which evaluates the frictional forces at the blood-endothelium interface, are 2 vascular targets for the physiopharmacologic approach to the treatment of hypertension. Improved arterial compliance has been found with both short- and long-term use of acebutolol, nicardipine and angiotensin-converting enzyme inhibitors, but not with atenolol, clonidine or propanolol. In addition, opposite effects on wall shear stress have been reported in studies using carteolol and atenolol. Shear rate and stress were significantly higher after carteolol than after atenolol, although both were associated with similar increases in blood viscosity. Therapy with acebutolol did not significantly increase wall shear rate or stress, nor did it increase blood viscosity. In conclusion, understanding the role of mechanical stresses in atherogenesis may result in more targeted prevention strategies to be applied in the treatment of hypertension.

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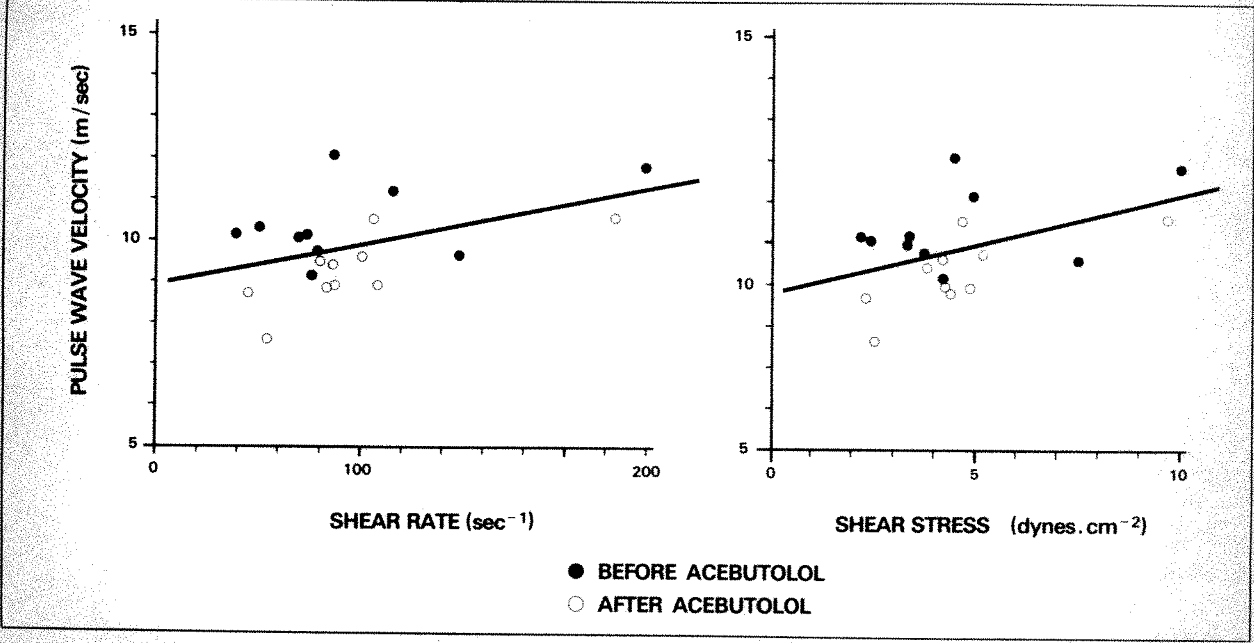

FIGURE 1. Relation between pulse-wave velocity, shear rate and shear stress during placebo and acebutolol administration ($r = 0.48$ and 0.46; $p < 0.05$, respectively).

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Documentation of the Effective Length of Action of Antihypertensive Treatment

Michael A. Weber, MD

The technique of automated ambulatory blood pressure (BP) monitoring offers an innovative means for measuring BP throughout the 24-hour period. Recently available compact monitoring instruments have been shown to be accurate and to provide reproducible measurements of the circadian BP pattern. The monitoring procedure is advantageous in that it minimizes or avoids placebo effects during therapeutic trials. Moreover, its power makes it possible to draw statistically valid conclusions regarding efficacy in fewer patients than would be required if conventional methods were used. This procedure also enhances the diagnosis of hypertension by identifying patients with "office" or "white coat" hypertension, and thereby facilitates assessment of treatment effects in those patients who are truly hypertensive. Automated monitoring measures BP at critical times of the day, including the preawakening and early morning hours, and it enables peak and trough antihypertensive drug effects to be carefully quantified. Since patient compliance appears to be enhanced with once- or twice-daily dosing, antihypertensive agents with long durations of action (24 hours) are of considerable interest. This report reviews some recent studies in which the monitoring technique has been used to measure the efficacy and duration of action of differing antihypertensive drugs.

(Am J Cardiol 1990;66:43C–48C)

Patients with mild to moderate hypertension are widely treated with antihypertensive drugs. There are several classes of agents with well-established blood pressure (BP)–lowering efficacy, and it is usually possible to select a drug that is effective and well tolerated for each patient. One of the major challenges in therapy is to maintain patient adherence to the treatment regimen on a long-term basis. Because hypertension is an asymptomatic condition, compliance with treatment requires strong motivation on the patient's part. Moreover, treatment should be simple and convenient, and there has been a growing interest by physicians in using drugs that are effective when administered just once or twice daily. Patients are more likely to adhere to their prescribed treatment if this type of simple regimen is prescribed; despite the enthusiasm of patients and physicians for drugs with relatively long durations of actions, there are concerns that some of these agents may not provide adequate BP control throughout the full 24-hour day.[1]

AMBULATORY BLOOD PRESSURE MONITORING TECHNIQUE

The availability of instruments that automatically measure BP levels throughout the day in patients undertaking their customary activities has enabled us to document the effects of antihypertensive agents. Because this methodology is still fairly new, it is helpful to consider briefly its chief characteristics. The modern ambulatory BP monitors are small, portable devices that use noninvasive cuff techniques to obtain repetitive BP measurements throughout a 24-hour period. Typically, these instruments perform their measurements at 15-minute intervals. There are 2 separate methods used by the modern monitoring devices: auscultatory and oscillometric. The auscultatory method employs a microphone or transducer positioned beneath the cuff that determines BP by listening for the Korotkoff sounds. Chest leads are used to obtain electrocardiographic R-wave gating for discriminating the true Korotkoff sounds. The oscillometric method depends on direct palpation of fluctuations within the brachial artery itself.

Although these approaches appear to be equally satisfactory, some investigators have demonstrated discrepancies between simultaneously obtained intraarterial and noninvasive methods.[2] Thus, reservations have been expressed about the validity and accuracy of the auscultatory and oscillometric noninvasive methods.[3] But scrutiny of these data suggests that although there may be differences between intraarterial and noninvasive readings, these differences appear to be reasonably consistent throughout the 24-hour period in individual subjects.[2]

It may actually be more relevant to compare BP levels measured by the portable instruments with those provid-

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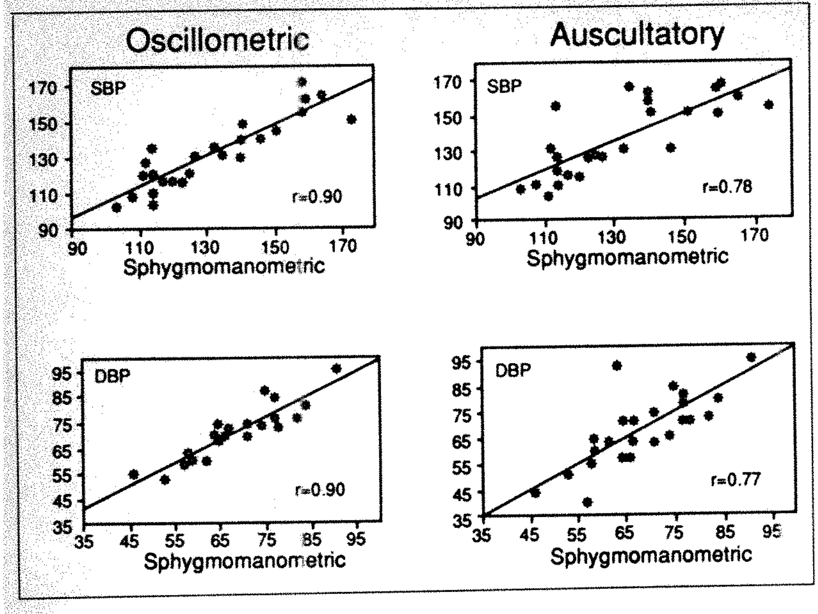

FIGURE 1. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) during 2 separate 24-hour monitoring periods, approximately 6 weeks apart, in 56 normal volunteers. Values shown are the means during each of the 12 periods of 2 hours' duration that comprise the whole day. (Reproduced with permission from *Am Heart J.*[4])

ed by the conventional mercury sphygmomanometer, for this standard instrument used in the office or clinic has been the basis for almost all major studies of clinical hypertension. Correlations between BP levels measured by auscultatory or oscillometric devices and those obtained with the mercury sphygmomanometer are shown in Figure 1.[4] These correlations are strong and provide confidence that the BP measured by the portable devices are a good reflection of conventionally measured values.

PHYSIOLOGIC APPLICATIONS OF MONITORING

Ambulatory BP monitoring units can be used either for diagnostic purposes or for evaluating the effectiveness of antihypertensive therapy. For both of these indications, however, it is important to justify the physiologic validity of the monitoring procedures. Studies of the clinical relevance of this technique have focused on 3 characteristics of the whole-day BP: its reproducibility, its ability to describe a circadian pattern and its relation to underlying cardiovascular status. The reproducibility of the 24-hour BP has been verified in studies using either intraarterial or noninvasive monitoring.[5,6] The actual circadian pattern of the BP, including the differences between daytime and nighttime values, appears to be highly reproducible and independent of the actual BP values themselves.[6] The 24-hour patterns of BP shown in Figure 2 were obtained in normal volunteers undergoing their routine daily activities. It is evident that the BP patterns during 24-hour monitoring periods separated by several weeks are superimposable.[6] This has particular relevance to studies of antihypertensive therapy, for it helps explain the absence of a placebo effect and thereby adds power to this method for discriminating the significance of even relatively modest treatment-induced changes in BP.

The characteristic pattern of BP describes a plateau during the daytime hours, followed by a decline to nadir values around midnight. The sharp early morning increase in BP that may originate before awakening and continues through to the early to midmorning hours is of interest. These morning BP changes probably reflect the parallel increase in sympathetic nervous system activity that is associated with the arousal process.[7] Increasing attention is being paid to these morning BP peaks, for it has been shown that a relatively large proportion of such major events as myocardial infarctions and strokes occur during this period.[8,9] Studies with ambulatory electrocardiogram monitoring also have confirmed the high prevalence of ischemic episodes at this time of day.[10] Again, this aspect of the 24-hour BP pattern is of potential importance to therapy, because therapeutic control of BP during this period of high vulnerability might be a key

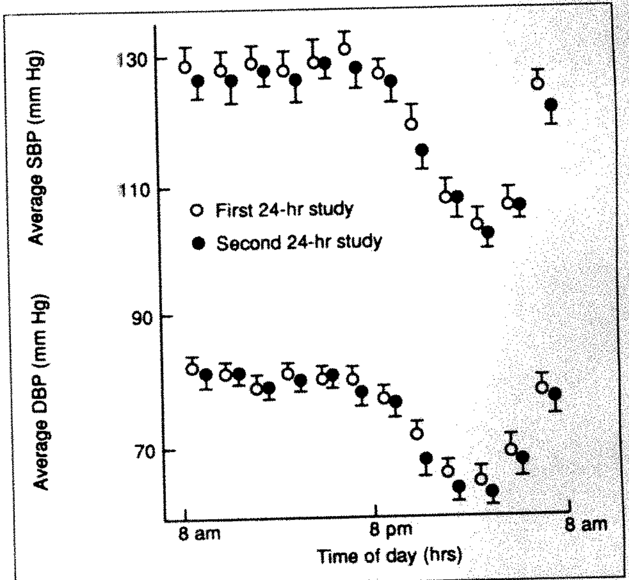

FIGURE 2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) during 2 separate 24-hour monitoring periods, approximately 6 weeks apart, in 56 normal volunteers. Values shown are the means during each of the 12 periods of 2 hours' duration that comprise the whole day. (Reproduced with permission from *Hypertension.*[18])

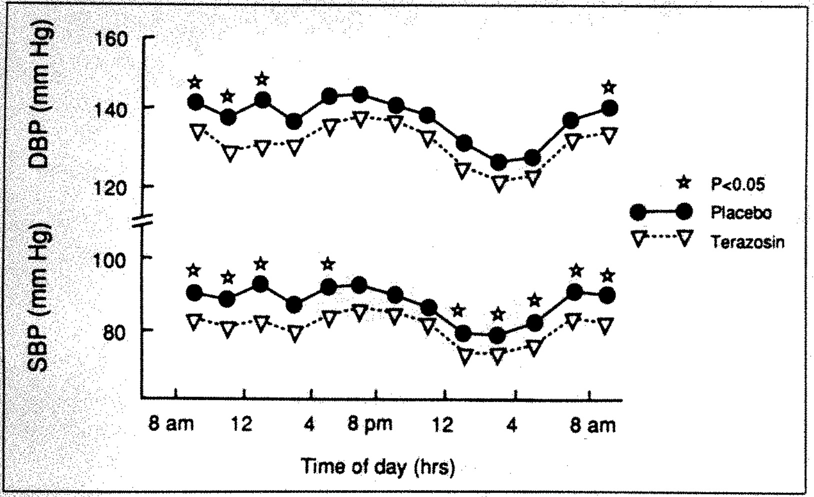

FIGURE 3. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values, shown as average 2-hour periods, during 24-hour automated ambulatory blood pressure monitoring, performed on 2 separate occasions 6 weeks apart, in 56 normal volunteers undergoing their routine daily activities. (Reproduced with permission *Arch Intern Med.*[19])

property of antihypertensive therapy directed at preventing cardiovascular events.

Finally, the relevance of the whole-day BP has been established in studies showing that it correlates more closely than conventional BP readings with evidence for changes in cardiovascular organs. It has been demonstrated, for example, that the readings obtained from automated BP monitoring predict echocardiographically measured left ventricular muscle mass far more closely than conventional readings.[10,11] Other studies that have focused on additional evidence for cardiovascular involvement, including changes in the optic fundi and clinical assessment of the heart and renal function, also have confirmed the clinical relevance of ambulatory BP monitoring.[12]

MEASURING ANTIHYPERTENSIVE EFFECTS

Unlike studies based on conventional office BP measurements, evaluations of antihypertensive therapy using ambulatory BP monitoring techniques do not show placebo effects.[13,14] The most likely explanation for apparent placebo response during standard therapeutic trials is that many participants enter the protocols with a misdiagnosis of hypertension. Some major studies have reported that the BP of >25% of patients, apparently hypertensive at baseline, become completely normal while the patient is taking placebo therapy.[15] The diagnostic problems of "office hypertension" or "white coat hyperten-

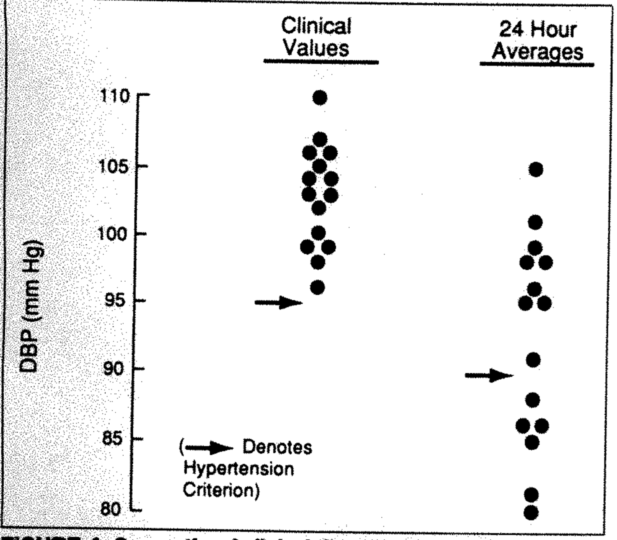

FIGURE 4. Conventional clinical diastolic blood pressure (DBP) measurements and 24-hour DBP averages in 15 hypertensive patients receiving placebo before a clinical trial. Values shown above the arrows indicate that the criterion for diagnosing hypertension (baseline DBP >95 mm Hg) was satisfied. (Reproduced with permission from *JAMA*.[20])

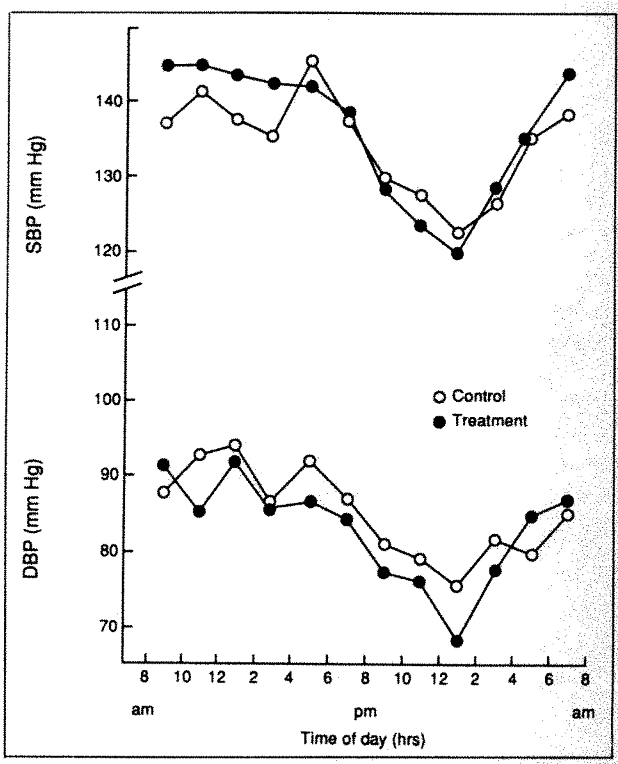

FIGURE 5. The 24-hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) values, given as averages for each of the 12 periods of 2 hours' duration that comprise the day, obtained at baseline (control) and during treatment with diltiazem in 6 patients whose hypertension was not confirmed by the baseline blood pressure monitoring. (Reproduced with permission from *JAMA*.[20])

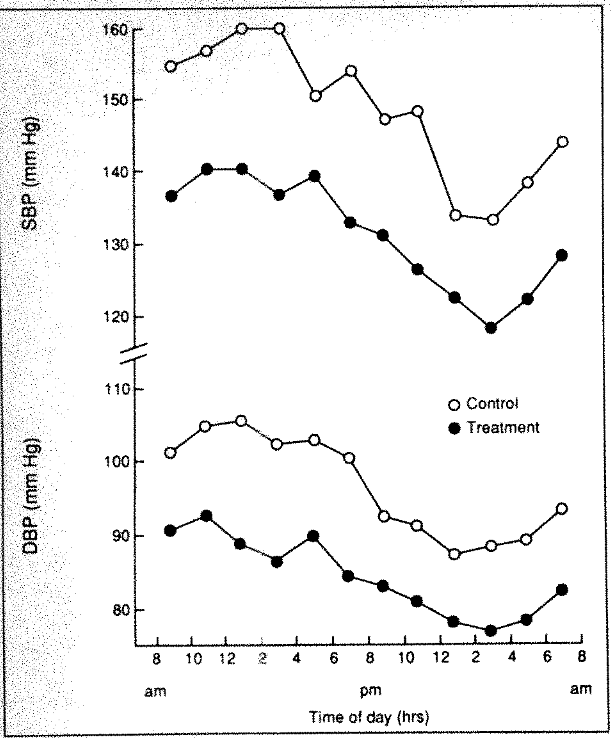

FIGURE 6. The 24-hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) values, given as averages for each of the 12 periods of 2 hours' duration that comprise the day, obtained at baseline (control) and during treatment with diltiazem in 9 patients whose hypertension was not confirmed by the baseline blood pressure monitoring. (Reproduced with permission from *JAMA*.[20])

sion" have been discussed in detail previously.[16-18] Because ambulatory BP monitoring accurately portrays the BP at the time of initial diagnosis and study entry, the apparent efficacy of placebo in patients with "white coat hypertension" is avoided.

The reproducibility or consistency of the ambulatory BP technique gives it the power to discriminate relatively modest changes in BP. Figure 3 shows a study performed in a small number of patients receiving low doses of the α-blocking agent terazosin once daily.[19] As expected, this low-dose monotherapy produced relatively small absolute decrements in BP; even so, the monitoring procedure had sufficient sensitivity to document the effects of the drug throughout the day. As a further practical issue, it has been shown that the power provided by the monitoring technique allows a statistically valid assessment of the effects of antihypertensive therapy to be determined in fewer patients than would be required if conventional BP measurements were the primary efficacy variable.[14]

DIAGNOSIS AND TREATMENT

As discussed earlier, a meaningful percentage of patients diagnosed as having hypertension by standard office methods appear to be normotensive when studied by 24-hour ambulatory monitoring. Thus, it is interesting to determine whether treatment administered to these "nonconfirmed" hypertensive patients has the same effect as in "true" hypertensive patients. Large BP decrements in "nonconfirmed" patients potentially could lead to problems of hypotension.

This issue was recently addressed in a study in which 15 patients were treated with the calcium channel-blocking agent diltiazem.[20] As shown in Figure 4, all 15 of these patients satisfied the office criterion of baseline diastolic BP >95 mm Hg. These readings were obtained at the end of a preliminary run-in period of several weeks, during which the patients received placebo. However, ambulatory BP monitoring was then performed as a baseline measurement before the initiation of active treatment. Figure 4 shows that 6 of the 15 patients failed to satisfy the monitoring criterion of hypertension despite the care with which they had been evaluated on entry into this study. As shown in Figure 5, treatment with diltiazem in the nonconfirmed group (n = 6) produced little if any antihypertensive effects. In contrast, this agent was clearly effective throughout the 24-hour period in 9 patients who had true hypertension (Fig. 6). These findings underscore the power of the monitoring technique to define antihypertensive efficacy in an individualized fashion in hypertensive patients.

FREQUENCY OF DOSING

One practical application of monitoring is to determine whether antihypertensive therapy can produce efficacy throughout the 24-hour period. This is of interest when drugs with intrinsically short durations of action are

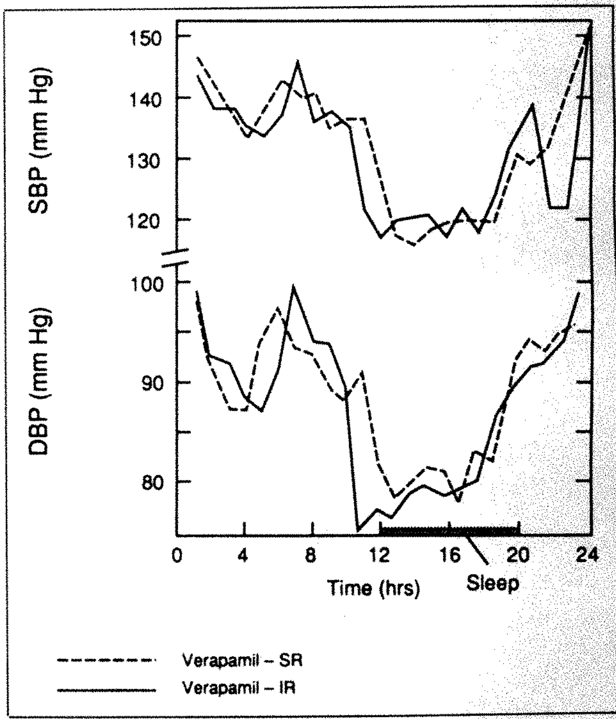

FIGURE 7. Mean automatic indirect blood pressure recordings in 8 patients receiving sustained-release verapamil (verapamil-SR) during double-blind phase. Initial recordings were made while patients were receiving regular-formulation verapamil (verapamil-IR) 3 times daily. The final automatic blood pressure recordings were carried out when once-daily sustained-release verapamil was administered. Zero represents the time between 8:00 A.M. and 9:00 A.M. (Reproduced with permission from *Am J Cardiol*.[21])

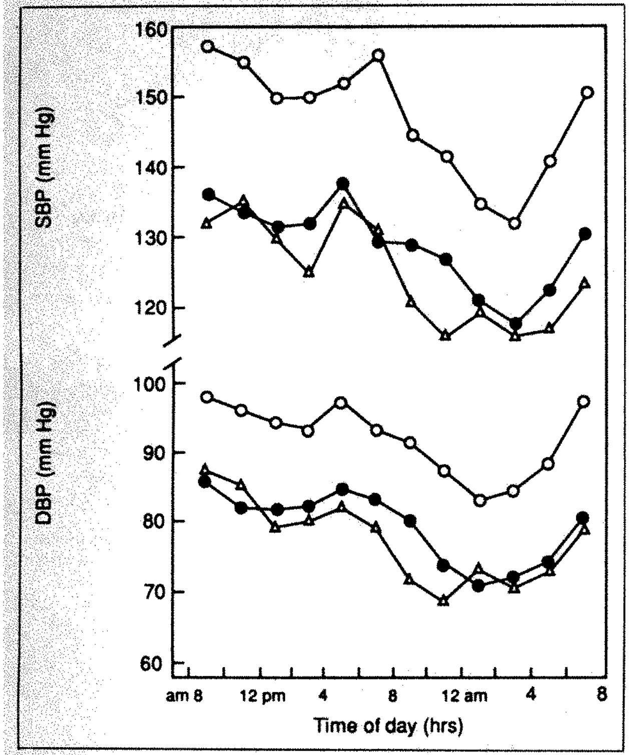

FIGURE 8. Whole-day systolic blood pressure (SBP) and diastolic blood pressure (DBP) values of treatment-responsive subjects receiving placebo (open circles) and during once-daily (solid circles) and twice-daily (triangles) therapy with captopril and hydrochlorothiazide. (Reproduced with permission from *Arch Intern Med*.[22])

reformulated, or made in combination with other agents, with the intention of providing 24-hour efficacy when administered just once daily. An example of this approach is shown in Figure 7.[21] In this study, patients were treated with the calcium channel-blocking agent verapamil. Ambulatory BP monitoring was performed while patients received either a short-acting immediate-release formulation of this agent given 3 times daily, or a long-acting sustained-release formulation given once daily. It is clear from Figure 7 that there is no difference between the 2 modes of treatment in their effects on BPs throughout the 24-hour period. These data thus provide evidence that the longer acting formulation is an adequate substitute for the immediate-release product despite being administered less frequently.

Another type of experience is shown in Figure 8.[22] In this study, performed in elderly patients, the angiotensin-converting enzyme inhibitor captopril was administered in combination with a low dose of the diuretic hydrochlorothiazide in a twice-daily dosing schedule. Compared with pretreatment baseline values, the combination therapy produced excellent control of BP throughout the day. Patients were then switched to once-daily administration of the same medication given in approximately the same total daily dose as when the treatment was given twice daily. The figure shows that the efficacy of the once-daily regimen is similar to that of the twice-daily regimen and provides effective control of BP for the full 24-hour period. This is an interesting observation, for captopril as single-agent therapy usually is administered twice daily to produce optimal effects. In combination with a low dose of diuretic, the ambulatory BP monitoring technique demonstrates 24-hour efficacy with a single daily dose.

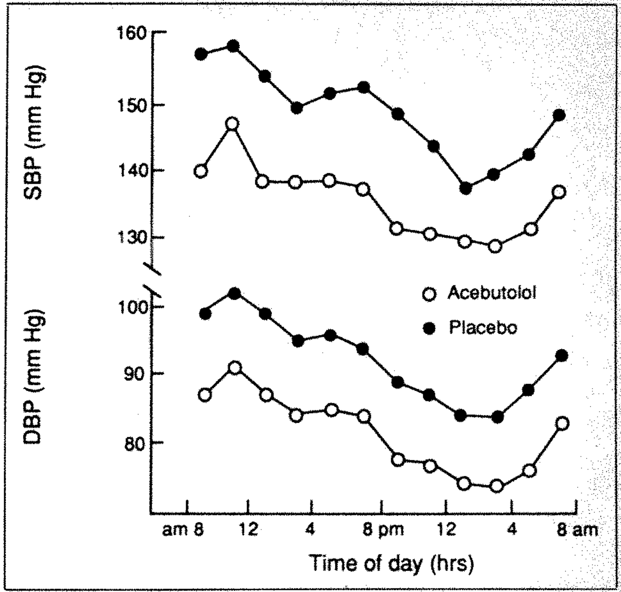

FIGURE 9. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values for 19 patients randomized to acebutolol. Values shown are the blood pressure averages for each of the 12 periods of 2 hours' duration that comprise the 24-hour ambulatory monitoring period. (Reproduced with permission from *Am Heart J*.[24])

PEAK AND TROUGH ISSUES

Peak effect, the maximum reduction in BP after administration of a drug, need not correspond to the time at which the drug's plasma concentration is at its highest level, although, in general, peak effect occurs relatively early during the dosing interval. By definition, the trough effect is the decrease in BP observed at the end of the dosing interval, immediately before administration of the next dose. Because once-daily drugs traditionally are administered in the morning, trough effects usually occur at that time of day (as discussed earlier) when the cardiovascular risk is highest. Thus, a meaningful control of BP at trough is an important property of an antihypertensive agent. Although the trough effect can be enhanced by increasing the size of the dose, this can create the danger of an excessive peak effect and the risk of early hypotensive responses. Because of this concern, the Food and Drug Administration has recommended that the ratio of trough to peak antihypertensive effects be at ≥1 to 2.[23]

A recent report has compared 2 β-blocking agents, acebutolol and atenolol, administered once daily to patients with essential hypertension.[24] Both drugs were clearly effective in decreasing BP, as shown by whole-day ambulatory BP monitoring. The data for acebutolol are shown in Figure 9. By comparison with the baseline BP measurements, the treatment values clearly were lower throughout the 24-hour period. Indeed, the baseline and treatment BP curves appear to be almost parallel to each other. The average decrease in diastolic BP for the day as

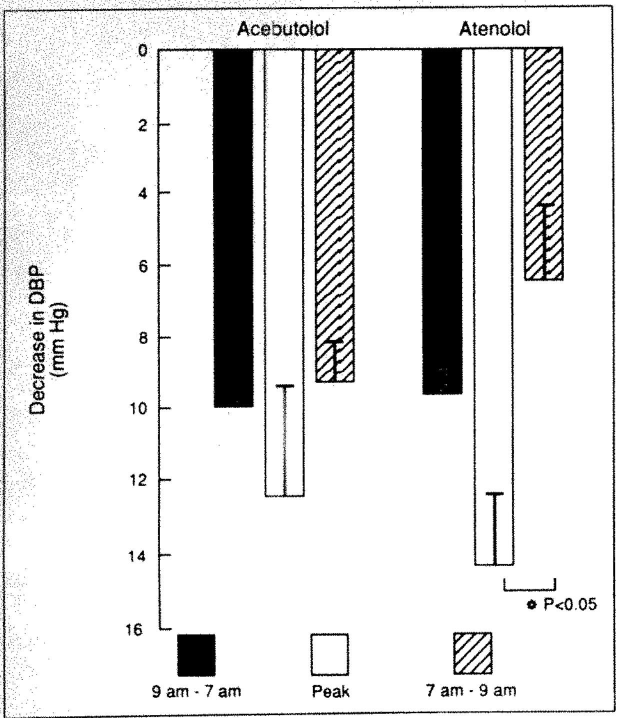

FIGURE 10. Average changes in diastolic blood pressure (DBP) during 24-hour monitoring procedures that began immediately after 9:00 α.μ. dosing with acebutolol (n = 19) or atenolol (n = 20). Data are shown for the first 22 hours (9:00 A.M. to 7:00 A.M.), the final 2 hours (7:00 A.M. to 9:00 A.M., trough) and the 2-hour period of maximum efficacy (peak). Values are mean ± standard error of the mean. (Reproduced with permission from *Am Heart J*.[24])

a whole was closely similar (approximately 10 mm Hg) for the 2 drugs.

The peak and trough data for the 2 agents are shown in Figure 10. To heighten accuracy of these measurements, data extracted from the whole day of monitoring are divided into 12 periods of 2 hours each: thus, the peak action of a drug occurs during that 2-hour period of the day that differs to a greater extent from its baseline value than any other 2-hour period, whereas the trough is the 2-hour period (7 A.M. to 9 A.M.) immediately preceding the next day's dose. For atenolol, the trough effect was significantly less than the peak effect, and the trough to peak ratio was approximately 43%. With acebutolol, the difference between trough and peak effects was not significant, and the ratio was 74%.

CONCLUSION

Previous reports by other investigators[1] have indicated that β blockers, as a class, might tend to lose their efficacy during the early morning hours. This, perhaps, reflects their inability to block norepinephrine-pressor effects, presumably mediated through arterial α receptors, that are associated with the morning surge of sympathetic activity. It is possible that acebutolol differs from other β blockers in some pharmacologic properties. It possesses intrinsic sympathomimetic activity and a long duration of action, permitting once-daily administration.

The recent report[24] comparing atenolol with acebutolol as assessed by whole-day ambulatory BP monitoring confirms the efficacy of these drugs in reducing BP. Acebutolol, however, was shown to be more effective than atenolol during the final 4 hours of therapy. Thus, acebutolol's BP-lowering effect was maintained throughout the full 24-hour period, including the critical morning hours when BP tends to increase rapidly. In comparison with other agents, acebutolol appears to be a β blocker with true 24-hour efficacy.

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Acebutolol Effects on Lipid Profile

Harold W. Schnaper, MD

The relation between lipid profile and the incidence of coronary artery disease has been confirmed by the results of epidemiologic and intervention studies. Among antihypertensive agents, β blockers, particularly those without intrinsic sympathomimetic activity (ISA), are generally reported to have negative effects on lipids, which may increase the risk of coronary artery disease. The ongoing Treatment of Mild Hypertension Study, now in its third year, has evaluated 847 patients to date with regard to lipid profile. Additional end points measured in this multicenter, randomized, controlled, double-blind study include blood pressure reduction and target organ deterioration. During the trial, all patients received nutritional and behavioral counseling to modify their diet, exercise habits and alcohol and sodium consumption to control their hypertension by nonpharmacologic means. In addition, some patients were randomized to receive low doses of 1 of the 5 classes of antihypertensive medication: acebutolol, a β blocker with ISA (n = 124); amlodipine, a calcium channel blocker (n = 122); chlorthalidone, a diuretic (n = 125); doxazosin, an α blocker (n = 128); enalapril, an angiotensin-converting enzyme inhibitor (n = 127) or placebo (n = 221). At 1 year, acebutolol showed a statistically significant (p <0.001) decrease in total cholesterol (−12.7 mg/dl) compared with placebo (−5.2 mg/dl) and with chlorthalidone (1.0 mg/dl); a significant (p <0.001) decrease in low-density lipoprotein cholesterol (−6.0 mg/dl) compared with placebo (+0.7 mg/dl) and with chlorthalidone (+8.0 mg/dl) and no change in high-density lipoprotein cholesterol (−0.4 mg/dl).

(Am J Cardiol 1990;66:49C–54C)

The increased risk of cardiovascular catastrophe with elevated total cholesterol levels has been documented repeatedly over the past 30 years. More recently, the availability of potent cholesterol-lowering agents has demonstrated the protective effect achieved by lowering elevated cholesterol levels. That approach to reducing cardiovascular risk is now widely accepted.[1]

The correlation between lipoprotein fractions—high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and very low-density lipoprotein (VLDL) cholesterol—and susceptibility to cardiovascular atherosclerotic deterioration has further advanced our understanding of cardiovascular risk. Higher levels of HDL and lower levels of LDL are associated with decreased cardiovascular risk; conversely, increased levels of LDL with concomitant decreases in HDL appear to increase the risk of atherosclerotic disease.[2–4] At present, no prospective clinical trial has demonstrated that manipulating those values confers greater protection, although it is accepted by some that routines and procedures that improve the HDL/LDL ratio are more beneficial than those that do not. Although a cause and effect relationship has not been established, results of clinical trials are consistent with the hypothesis that HDL in some way is "protective" against the development of atherosclerosis.[1]

This better understanding of the risks associated with the cholesterol-carrying lipoprotein moieties has raised the concern that certain medications requiring long-term administration, such as antihypertensive agents, may cause unfavorable lipoprotein patterns.[5] The classes of antihypertensive agents that have been shown to have adverse effects on cholesterol levels are among those that have been available longest and are most widely used, including the diuretics and the first- and second-generation β-blocking agents. A 5 to 10% sustained increase in cholesterol levels appears to accompany treatment with those medications. It has been suggested that such drug-induced changes in cholesterol, as well as the adverse changes in the HDL/LDL ratio, may offset some or all the protection against coronary atherosclerosis that is afforded by blood pressure reduction.[5] Other β blockers that possess intrinsic sympathomimetic activity (ISA), such as pindolol and acebutolol, appear to have a more favorable effect on lipid profile. Acebutolol belongs to a new class of β blockers that possess peripheral vasodilating effects. The newer agents appear to have advantages over older β blockers in terms of reduced clinical adverse effects on lipid profile, and their blood pressure-lowering ability is well documented. Unlike traditional β blockers, acebutolol has been shown to decrease total cholesterol levels and improve the HDL/LDL ratio while effectively reducing blood pressure.[6]

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TABLE I Acebutolol Studies Published Before 1988

Study	Design	Duration (months)	No. of Pts Studied: Acebutolol	No. of Pts Studied: Other drug
Ieri et al (1985)	Open	12	17	
Lehtonen (1984)	Open	6	18	
Matsumoto and Nakamura (1986)	Retrospective	≥12	28	9 (propranolol) 18 (pindolol)
Jiao et al (1986)	Open	2	9	
Giuntolli et al (1984)	Open	12	15	
Birnbaum et al (1983)	Randomized crossover	2	20	20 (propranolol)
Wahl et al (1986)	Parallel group	6	182	178 (hydrochlorothiazide)
Jaillard (1982)	Open	6	20	
Rouffy (1984)	Parallel group	3	10	10 (placebo)
Scotti et al (1983)	Open	2	202	
Hagel and Ulm (1983)	Parallel group	2	10	10 (penbutolol)
Lehtonen (1985)	Open	6	18	
Nakamura (1987)	Nonrandomized crossover	3	11	11 (propranolol)
Miller et al (1987)	Parallel group	12	8	7 (propranolol)
Miller (unpublished data)	Randomized crossover	1.5	16	16 (propranolol)

Adapted from *Drugs*.[6]

TABLE II TOMHS: Change in Total Cholesterol (mg/dl) from Baseline

Treatment Group	No.	Baseline Mean (SD)	Change* Mean (SD)
Acebutolol	124	232 (40)	−13 (26)
Amlodipine	122	229 (42)	−7 (29)
Chlorthalidone	125	231 (39)	1.0 (26)
Doxazosin	128	229 (38)	−13 (26)
Enalapril	127	226 (37)	−8 (24)
Placebo	221	225 (37)	−5 (23)

* Chlorothalidone vs each of the active treatments ($p < 0.01$).

TABLE III TOMHS: Change in Low-Density Lipoprotein Cholesterol (mg/dl) from Baseline

Treatment Group	No.	Baseline Mean (SD)	Change* Mean (SD)
Acebutolol	124	162 (35)	−6.0 (26)
Amlodipine	122	159 (38)	−0.8 (25)
Chlorthalidone	125	161 (35)	+8.0 (26)
Doxazosin	128	158 (35)	−4.9 (24)
Enalapril	127	153 (34)	−1.7 (23)
Placebo	221	157 (33)	+0.7 (22)

* Chlorothalidone vs acebutolol, doxazosin and enalapril ($p < 0.01$).

The Treatment of Mild Hypertension Study (TOMHS) is a multicenter, randomized, controlled, double-blind trial that is currently being conducted to compare the effects of nonpharmacologic therapy alone with those obtained when active drug therapies are combined with nonpharmacologic therapy in patients with mild hypertension. All patients received nutritional and behavioral counseling to control their hypertension by nonpharmacologic intervention, including weight loss, increase in physical activity and reduction of sodium and alcohol intakes. The 5 medications were selected to be representative of each of the major classes of antihypertensive agents. Patients entering the study were randomized to receive low doses of 1 of the 5 classes of antihypertensive medication: acebutolol, a β blocker with ISA ($n = 124$); amlodipine, a calcium channel blocker ($n = 122$); chlorthalidone, a diuretic ($n = 125$); doxazosin, an α blocker ($n = 128$); enalapril, an angiotensin-converting enzyme inhibitor ($n = 127$) and placebo ($n = 221$).

ACEBUTOLOL'S EFFECTS ON TOTAL CHOLESTEROL

Fifteen clinical trials with acebutolol that included evaluation of its effects on lipid fractions have been reviewed by Clucas and Miller (Table I).[6-20] In most of those studies, total cholesterol levels remained unchanged with acebutolol; however, 3 studies shostatistically significant decreases. A comparison of acebutolol's effect on

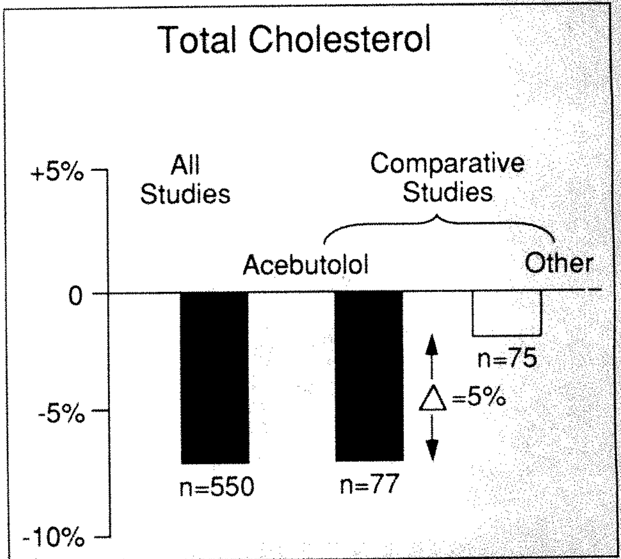

FIGURE 1. Percent change in total cholesterol levels in studies with acebutolol alone and acebutolol in comparison with propranolol, pindolol, hydrochlorothiazide or penbutolol. (Adapted from *Drugs*.[6])

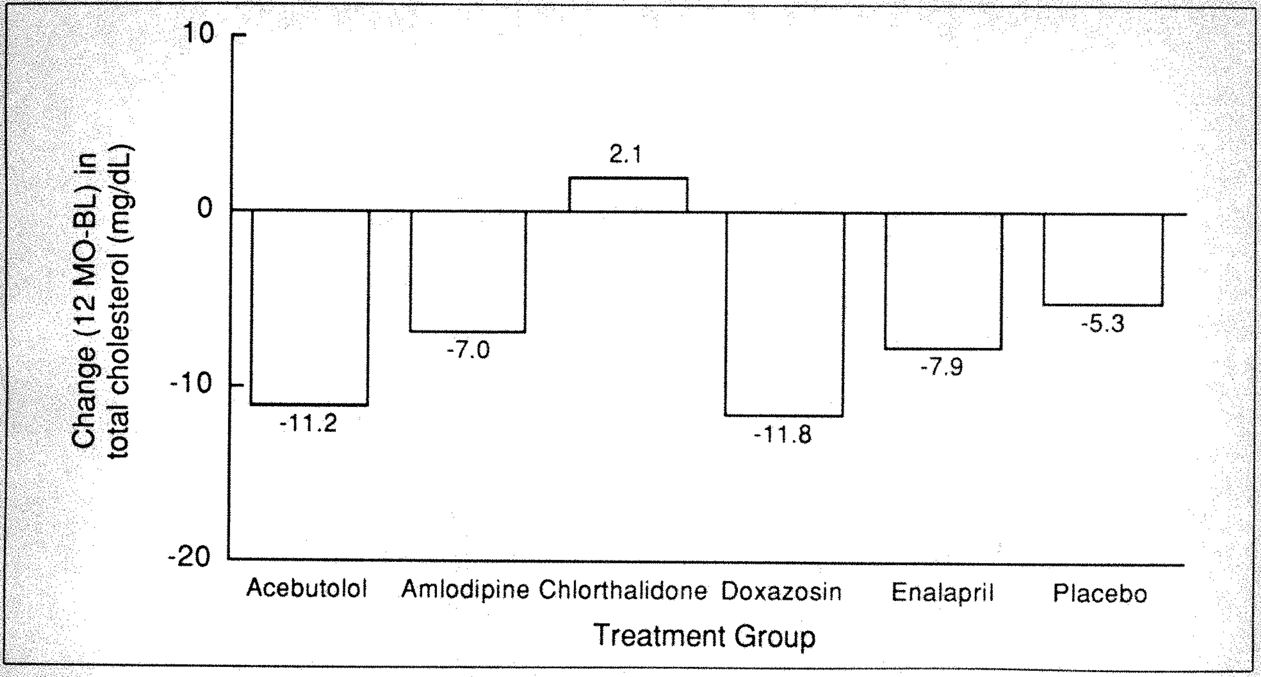

FIGURE 2. TOHMS data showing change in total cholesterol level (mg/dl) from baseline to 1 year. Acebutolol vs placebo, p <0.001. MO-BL = 12 months-baseline.

total cholesterol compared with those of other agents is shown in Figure 1. Acebutolol lowered cholesterol by approximately 7%, a 2.5-fold greater reduction than was obtained with other agents, which lowered cholesterol by only 2%.

Data from TOMHS indicate that acebutolol decreased total cholesterol levels significantly ($p < 0.001$) when compared with placebo and diuretic therapy. The change from baseline in total cholesterol level achieved with each active drug or placebo plus nonpharmacologic intervention is shown in Table II. Changes from baseline only at 1 year are shown in Figure 2. Acebutolol's decrease from baseline of 12.7 mg/dl was approximately 2.3 times greater than that obtained with nonpharmacologic intervention alone, which lowered cholesterol by only 5.2 mg/dl. Acebutolol's effect was matched by doxazosin but was not matched by any of the other medications, and the changes in cholesterol levels achieved with acebutolol and doxazosin were considerably lower than those obtained with placebo or the other active medications ($p < 0.001$). At 1 year, chlorthalidone increased the cholesterol level over placebo by 7.5 mg/dl ($p < 0.01$). This increase was sustained over the 1-year period, as shown in Figure 2.

ACEBUTOLOL'S EFFECTS ON LOW-DENSITY LIPOPROTEIN

In the analysis of Clucas and Miller,[6] acebutolol was associated with a favorable 5% decrease in LDL when administered alone or compared with placebo; when compared with other agents, the decrease of 10% was 4 times greater than the change achieved with the comparative agents, which lowered cholesterol by only 2% (Fig. 3). Table III and Figure 4 show 1-year data from TOMHS regarding changes in LDL with the 5 agents and placebo.

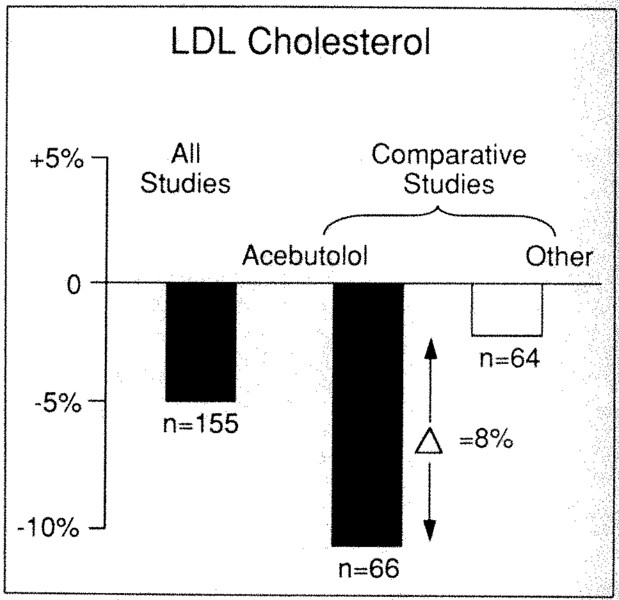

FIGURE 3. Percent change in low-density lipoprotein (LDL) levels in studies with acebutolol alone and in comparison with other agents. (Adapted with permission from *Drugs*.[6])

Acebutolol therapy decreased LDL level over placebo by 6.7 mg/dl. Again, as with the total cholesterol level, the 8.0 mg/dl increase from baseline in LDL associated with chlorthalidone therapy was sustained over the 1-year period (Fig. 4).

ACEBUTOLOL'S EFFECTS ON HIGH-DENSITY LIPOPROTEIN

Figure 5 shows the relationship between HDL level and mortality risk. Those data, from the Framingham Study,[4] demonstrate that mortality risk from cardiovas-

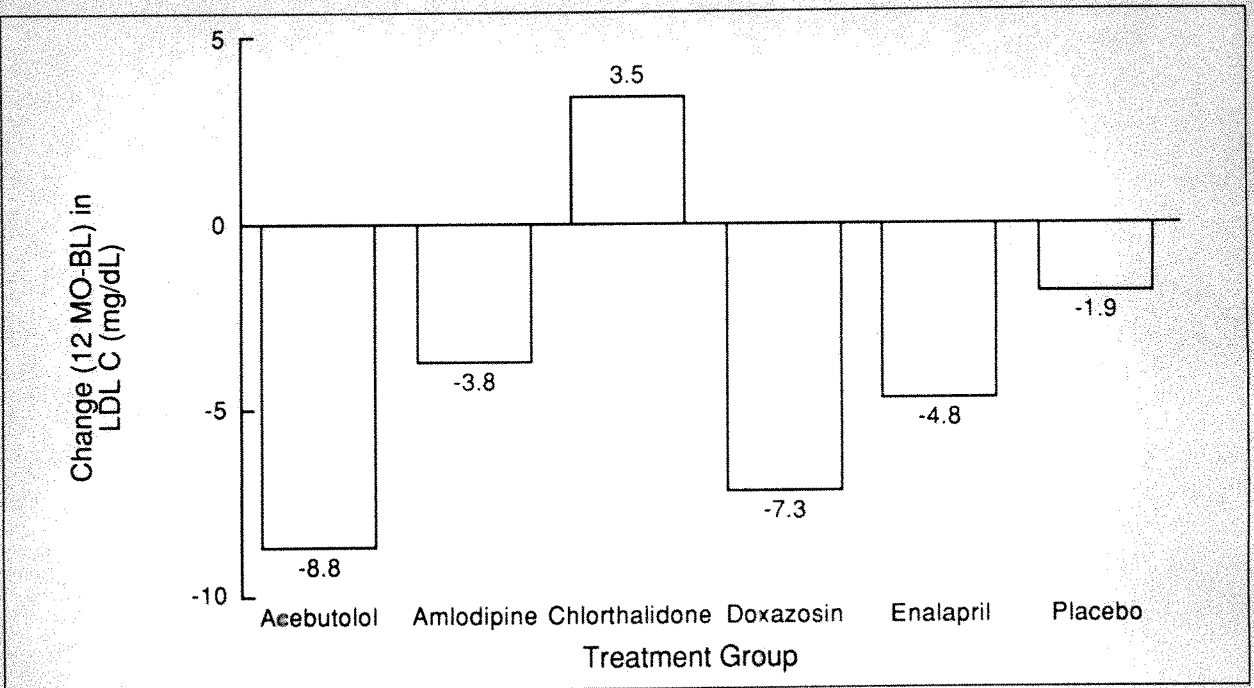

FIGURE 4. TOHMS data showing change in low-density lipoprotein (LDL) level (mg/dl) from baseline to 1 year. Acebutolol vs placebo, p <0.001. C = cholesterol; MO-BL = 12 months-baseline.

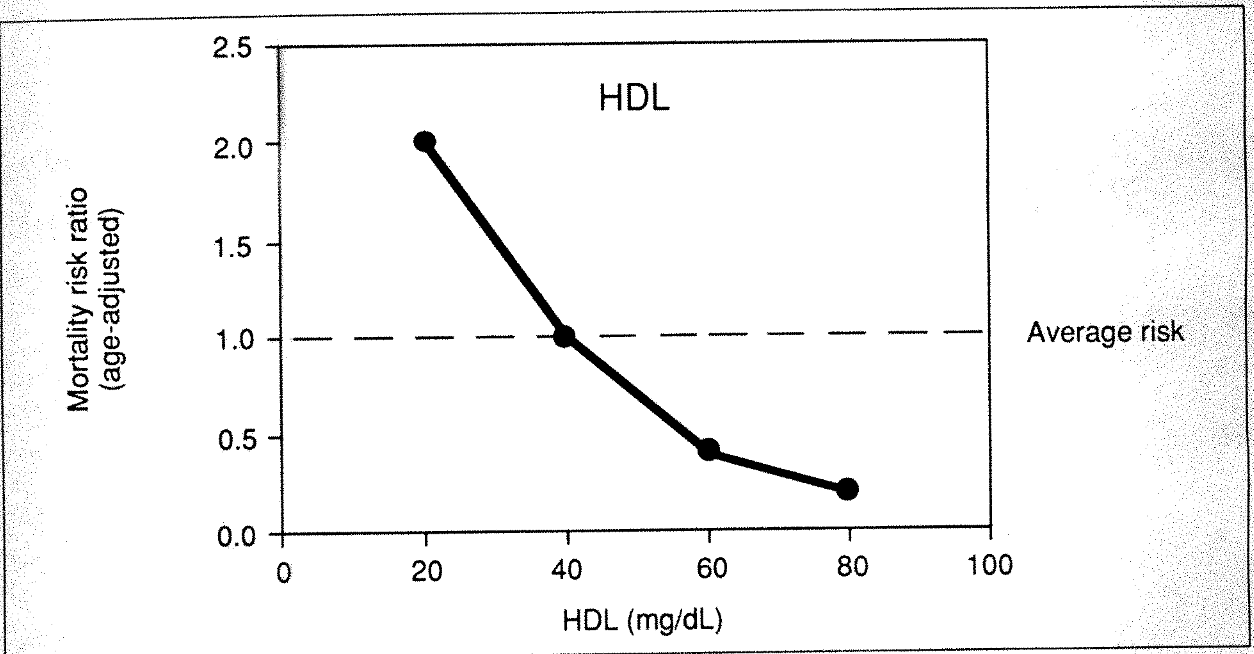

FIGURE 5. Relationship between high-density lipoprotein (HDL) levels and age-adjusted mortality risk. (Adapted from *Am J Med.*[4])

cular disease increases as levels of HDL decrease. The average risk of mortality from cardiovascular disease is at a level of 40 mg/dl; risk decreases by one fourth as the level of HDL increases to 80 mg/dl.

Analysis of the effect on HDL in the 15 trials published before 1988 (Fig. 6) reveals acebutolol increased HDL levels vs placebo by approximately 1.5%, whereas the other β blockers, particularly during long-term therapy, caused little change or resulted in a decrease in HDL. Overall, the other medications decreased HDL levels by approximately 6%; thus, therapy with acebutolol resulted in a beneficial increase in HDL levels while other medications tended to decrease HDL levels.

A similar trend is observed in the TOMHS data at 1 year: the actual change in HDL level with acebutolol therapy was nonsignificant from baseline, and none of the other medications showed changes significantly different from baseline (Table IV). With placebo alone (coupled with nonpharmacologic intervention), the increase in HDL level from baseline was 1.6 mg/dl. Figure 7 illus-

TABLE IV TOMHS: Change in High-Density Lipoprotein Cholesterol (mg/dl) from Baseline

Treatment Group	No.	Baseline Mean (SD)	Change Mean (SD)
Acebutolol	124	44 (13)	−0.4 (7)
Amlodipine	122	44 (10)	2 (7)
Chlorthalidone	125	44 (11)	2 (8)
Doxazosin	128	45 (11)	2 (7)
Enalapril	127	44 (12)	3 (6)
Placebo	221	43 (12)	2 (7)

trates the change in ratio of HDL to total cholesterol from baseline to 1 year. Acebutolol therapy resulted in a 0.8% change; the greatest change, 2.3%, was achieved with doxazosin therapy. Thus, acebutolol's net effect on lipid profile is at least neutral, given the modest change in HDL and the marked decrease in LDL observed in the TOMHS trial. Those results appear to corroborate data from the 15 studies published before 1988. When compared with other antihypertensive agents, acebutolol appears to have no adverse effects on serum lipid profile.

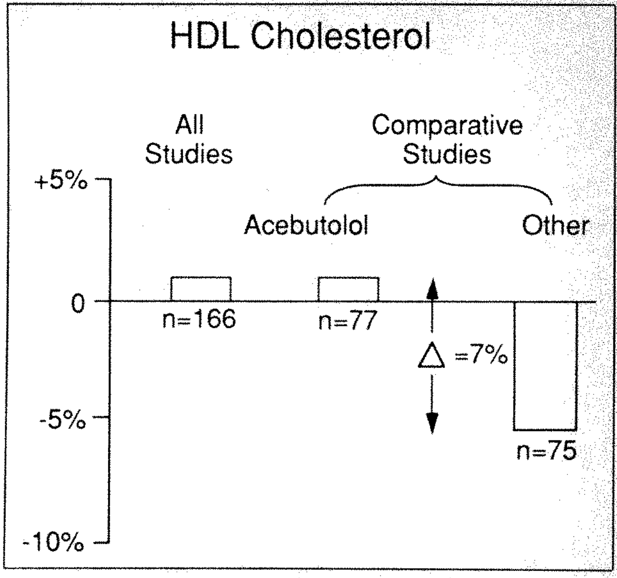

FIGURE 6. Percent change in high-density lipoprotein (HDL) cholesterol level in studies with acebutolol alone and in comparison with other agents. (Adapted from *Drugs*.[6])

CONCLUSION

Hypertension is a major risk factor for atherosclerosis, and the effective reduction of elevated blood pressure levels through diet, behavior modification or the judicious use of antihypertensive medications may be credited with the decreased mortality rate observed in atherosclerotic patients over the past 30 years. Controlled long-term clinical trials show that antihypertensive treatment is more effective in reducing death due to stroke than in reducing death due to coronary artery disease.[5] In recent years, concern has been expressed about the safety of specific antihypertensive agents, particularly diuretic therapy, and the ability of antihypertensive treatment to prevent coronary and cardiovascular disease.[5] The pattern of lipid changes observed from the results of TOMHS after 1 year of acebutolol treatment appears to corroborate earlier data that showed that acebutolol has no adverse effects on lipids, and indeed may have a protective effect against risk of cardiovascular disease. Long-term results of TOMHS will help clarify the optimal treatment of hypertension with regard to lipid profile as well as risk predictions based on drug-induced changes in lipid metabolism.

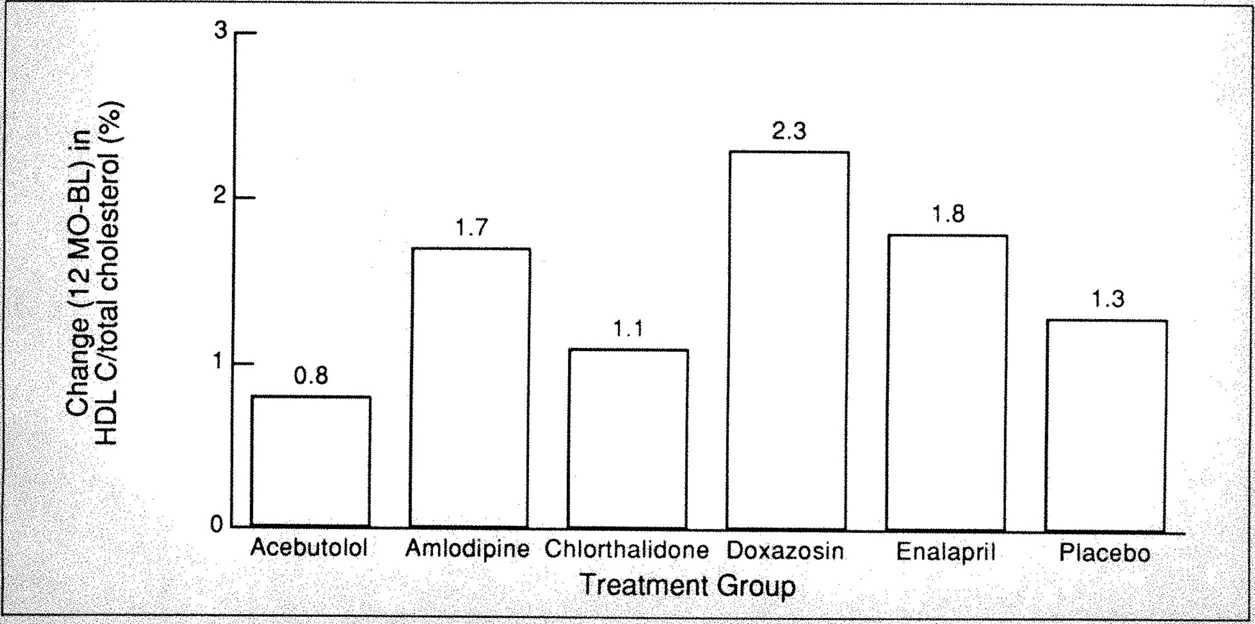

FIGURE 7. TOHMS data showing change in ratio of high-density lipoprotein (HDL) cholesterol (C) to total cholesterol from baseline to 1 year. MO-BL = 12 months-baseline.

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Conclusions

Stanley H. Taylor, PhD, MD, and William H. Frishman, MD

Beta-adrenoceptor antagonists were specifically developed by Sir James Black for the treatment of ischemic heart disease. Fortuitously, they were found to be efficacious in patients with high blood pressure and certain ventricular arrhythmias. The highlight of their clinical deployment, however, was the demonstration that these agents had the potential to extend lifespan in survivors of myocardial infarction (MI) without seriously inhibiting these patients' quality of life. This promise was confirmed for nonselective β-blocking drugs without either cardioselectivity or intrinsic sympathomimetic activity in 2 large, well-designed and well-executed clinical trials. The doubts that arose, particularly with regard to the preventive inadequacy of β-blocking drugs with intrinsic sympathomimetic activity, was based on a number of less well-designed and less extensive trials. The failure to demonstrate a clear-cut preventive property with these latter drugs was attributed to their pharmacologic characteristics, particularly with regard to the presence of intrinsic sympathomimetic activity. However, we now know that such beliefs are unfounded, and the results of the Acebutolol et Prévention Secondaire de l'Infarctus (APSI) study reported in this symposium confirm such a statement. It is now reasonable to accept that the preventive potential of β-blocking drugs in patients who have survived MI is a class response, irrespective of the ancillary pharmacologic properties of β-blocking drugs.

The APSI study, however, extends knowledge in 1 very important additional clinical direction. The earlier preventive studies with β-blocking drugs in survivors of acute MI were concerned with relatively low-risk cases without severe myocardial damage. This was a reasonable approach when the studies were first conceived, due to the theoretical risk of the precipitation of heart failure in patients with extensive myocardial damage. Fortunately, this has not proved to be the case, and the APSI study clearly demonstrates the beneficial effect of acebutolol in high-risk survivors of MI.

There are a number of other potential benefits to consider with acebutolol. The drug has the desirous pharmacologic profile of β_1 selectivity with moderate partial agonist sympathomimetic activity. Thus, it can be expected to have fewer deleterious effects on systemic vascular resistance than β-blocking drugs without intrinsic sympathomimetic activity. Levenson and colleagues also report in this symposium the beneficial influence of acebutolol on systemic arterial wall stiffness, an important factor contributing to the work of the heart. The property of intrinsic sympathomimetic activity also endows acebutolol with another vital preventive element not possessed by nonselective β-blocking drugs, namely the ability to beneficially modulate the plasma lipid profile. In fact, Schnaper in this symposium reports that the reduction in plasma total cholesterol induced by acebutolol was equivalent to that which one would expect with many of the commonly used specific anticholesterolemic drugs. Moreover, the reduction in total plasma cholesterol concentration was achieved by the most advantageous change in the profile of its components—a reduction in the low-density lipoprotein cholesterol fraction and no change in the high-density lipoprotein fraction. In patients at high risk from further MI, such modulation of the total plasma cholesterol and its components can be expected to extend the preventive influence of β blockade on the heart.

Taking into account these various aspects, it would be reasonable to express the opinion that the prolongation of lifespan following acute MI endowed by the β-blocking drugs is a class effort, and the ancillary pharmacologic properties of cardioselectivity and intrinsic sympathomimetic activity, far from being deleterious, may in fact have further preventive potential in high-risk patients. Furthermore, the fact that mortality is further significantly reduced if the drug is being taken at the time of the next MI underlines the important therapeutic significance of the APSI trial reported in these proceedings.

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A Symposium: Triggering and Circadian Variation of Onset of Acute Cardiovascular Disease

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NOVEMBER 6, 1990 VOL. 66 NO. 16

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Introduction

James E. Muller, MD, and Geoffrey H. Tofler, MB

This symposium issue of the *American Journal of Cardiology* provides the first compilation of reports in the emerging field of study of triggering and circadian variation of onset of acute cardiovascular disease. These reports were prepared by researchers who participated in 2 symposia dedicated to this topic (Boston, Massachusetts, February 25, 1989; and Phoenix, Arizona, May 5 and 6, 1989). The symposia were supported by an educational grant from Bristol-Myers Squibb Company. The variety of ideas expressed in this issue reflect the stimulating interchange that occurred among researchers approaching this new topic from different disciplines.

The relation of this new field of study to the traditional areas of research on coronary artery disease is shown in Figure 1. Great progress has been made in the identification of chronic risk factors for arterial thrombosis, in the treatment of acute thrombosis and long-term management after the acute event. The new area of research focuses on the hours and minutes before the onset of occlusive arterial thrombosis—on the conversion of chronic to acute disease. The recognition of circadian variation and the possibility of frequent triggering provide new information suggesting the value of study of this time period. It is the hope of researchers that findings in this new area may make it possible to transform the gains achieved in the 1980s in traditional areas of research into more effective preventive measures.

The reports are grouped into 5 categories reflecting different approaches to the issue: epidemiologic findings, transient myocardial ischemia, angiographic and pathologic findings, physiologic mechanisms and results of pharmacologic intervention. The purpose of this introduction is to summarize the contents of the supplement and to add the information—old and new—required for a complete presentation of this new approach to prevention of onset of cardiovascular disease.

EPIDEMIOLOGIC FINDINGS

The objective evidence documenting the circadian variation of onset of acute myocardial infarction[1] is presented in Figure 2. Numerous prior publications had reported a morning increase in the onset of symptoms of myocardial infarction,[2,3] but had received little attention, presumably because symptoms were used to time onset of the event. All prior studies were subject to the criticism

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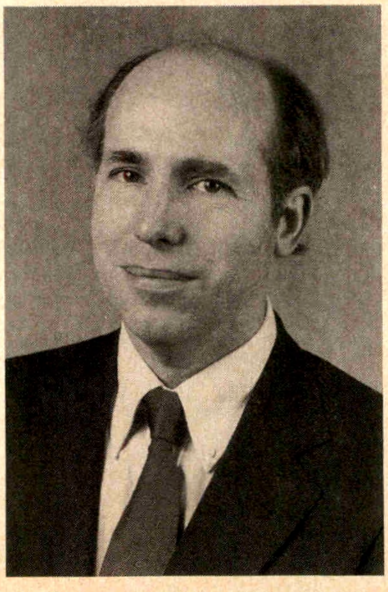

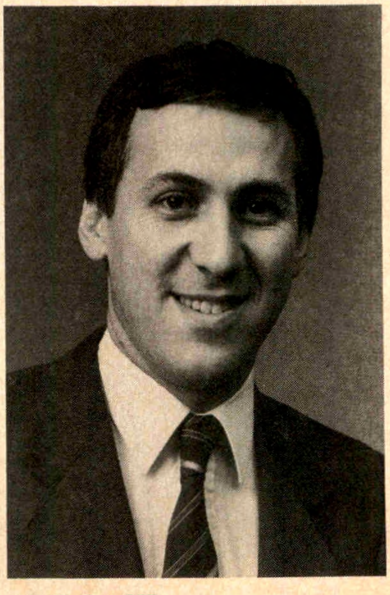

***Left,* James E. Muller, MD; *right,* Geoffrey H. Tofler, MB**

that many patients may have been asleep at the onset of myocardial infarction, and hence the increased morning incidence was simply an artifact of delayed recognition of onset at the time of awakening. The data shown in Figure 2 from the Multicenter Investigation of Limitation of Infarct Size (MILIS) study were based on time of appearance of creatine kinase (CK) in plasma, and were not subject to such an interpretation. They have subsequently been confirmed by similar data obtained from the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) study,[4] and supported by the rapidly accumulating parallel data showing morning increases for onset of many types of cardiovascular disease.

The MILIS data also showed a strong correlation between symptom-timed and CK-timed onset ($r = 0.85$), indicating that analysis of time of symptom onset in large groups of patients might indeed be of value. In this supplement, Gilpin et al report time of onset of symptoms of myocardial infarction in a study sufficiently large (4,796 patients) to determine the pattern of onset in various subgroups. While the overall population demonstrated a primary morning peak and a smaller secondary evening peak in incidence similar to prior reports, interesting variations were found in certain subgroups. Patients with prior congestive heart failure, or who experienced a non-Q-wave infarction, had a primary peak in the evening; those over 70 years of age, smokers, diabetics, women and patients taking β-adrenergic blocking agents had 2 relatively equal peaks; and those with prior infarction had no peaks. The report by Gilpin et al that prior β-blockade therapy resulted in similar morning and evening peaks is compatible with the findings in the MILIS and ISAM databases that prior β blockade abolished the prominent morning peak in infarct onset.

Psaty et al report data in hypertensive patients relevant to the mechanism of the cardioprotective action of β blockers (and presumably also relevant to their ability to alter the time of day of onset of infarction). They found that β-blockade therapy was associated with a 38% reduction in the incidence of a first nonfatal myocardial infarction. In addition, protection was associated with the use of β blockers in a dose-response fashion—a finding compatible with the hypothesis that β blockers prevent infarction by interrupting the consequences of an external triggering event.

In the final portion of the epidemiologic section, Willich presents data indicating that sudden cardiac death occurs with a circadian pattern similar to that of nonfatal infarction. This is not a surprising finding for sudden death due to occlusive thrombus formation since, in most cases, a detectable infarct would have occurred, had the patient lived. However, since only approximately one-third of the cases of sudden cardiac death have an occlusive coronary thrombus at autopsy, the similar circadian patterns for the entire group suggest either that the plaque rupture and subsequent thrombosis formation, ischemia and sudden-death scenario is quite frequent, as suggested by Davies and Thomas,[5] or that primary ar-

Chronic risk factors	Conversion of chronic to acute disease	ONSET OF THROMBOSIS	Acute treatment	Prognosis
Age			Thrombolysis	Post MI ETT
Cholesterol			Treatment of arrhythmia	ASA
High BP			PTCA	Beta blockade
DM	Circadian variation		Beta blockade	E.P. testing
Fibrinogen	Triggers			CABG
				Holter monitoring
→	→		→	→
Years, months	Hours, minutes		Minutes, hours	Days, years

FIGURE 1. Research on coronary artery disease. Relation of the field of study of conversion of chronic to acute disease, including circadian variation and triggering of acute cardiovascular disease, to traditional areas of research on coronary artery disease.

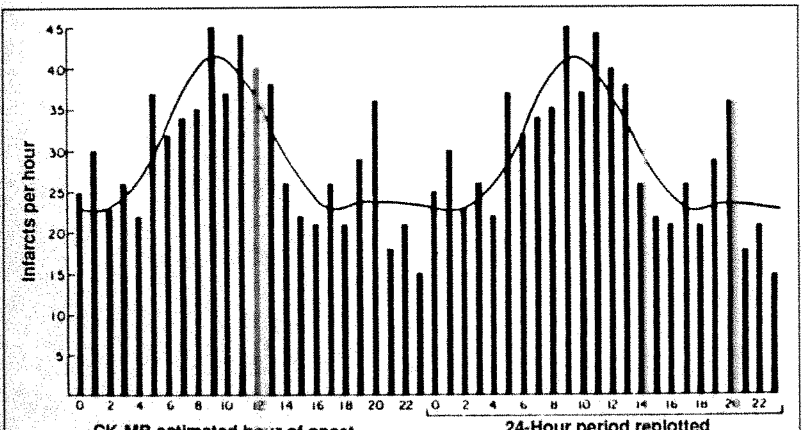

FIGURE 2. The hourly frequency of onset of myocardial infarction as determined by the creatine-kinase-MB (CK-MB) method in 703 patients. A 2-harmonic regression equation has been fitted to the data (*curved line*). A prominent circadian rhythm is present, with a primary peak incidence of infarction at 9 A.M. and a smaller secondary peak at 8 P.M. (Adapted from *N Engl J Med.*[1])

rhythmic sudden death is also more likely in the morning. The latter possibility is supported by data indicating a prominent morning increase in ventricular tachycardia.[6]

While informative, the epidemiologic studies conducted thus far provide only an introduction to the topic, since time of day is likely to be primarily a surrogate for the activity-rest cycle. This view is supported by data from Goldberg et al,[7] who have demonstrated that the increase in onset of nonfatal myocardial infarction occurs in the first hour after awakening. A National Heart, Lung, and Blood Institute-funded study is currently in progress in which over 3,000 patients will be interviewed to determine their activities immediately before infarction onset (Myocardial Infarction Onset Study). Activity before infarction will be compared with activity in a control period to determine relative risk of various exposures, using a "case-crossover" method developed by Maclure[8] of the Harvard School of Public Health. With such an approach, it will be possible to evaluate the frequent reporting by patients of possible triggers of infarction noted by Tofler et al[9] and determine the frequency of the exceptional cases in which a trigger is easily recognized.[10]

TRANSIENT MYOCARDIAL ISCHEMIA

The timing and triggering of transient myocardial ischemia can be studied much more easily than the rarer, catastrophic disorders of myocardial infarction and sudden cardiac death. With continuous 24-hour ambulatory electrocardiographic monitoring, it has been shown conclusively, as presented by Rocco in this supplement, that episodes of transient myocardial ischemia have a circadian pattern similar to that of myocardial infarction. In the report of Rocco, the increase is shown to occur in the hours after awakening, as it does for infarction. With the use of diaries, it was possible to normalize the frequency of ischemia after a potential trigger for the time spent exposed to the trigger. This demonstrated the high frequency of mental stress as a trigger.

The report by Coy et al illustrates the use of specialized mathematical methods (time-series analysis) to evaluate temporal patterns of transient ischemic episodes. The analysis revealed a 24-hour periodicity without β-blockade therapy and a 5- to 8-hour periodicity after β-blockade therapy. Deedwania has measured ambulatory systemic arterial blood pressure and has shown that the majority of attacks of ischemia are preceded by an increase in myocardial oxygen demand. Bairey et al report on the high frequency of induction of ventricular wall motion abnormalities by mental stress. Furthermore, the occasional marked surges in arterial pressure observed after mental stress could contribute to triggering of onset of infarction by relatively inconspicuous processes. Finally, Stone reports on a study demonstrating that β-adrenergic blockade can reduce the occurrence of morning ischemia without eliminating the morning increase in platelet aggregability. Stone also examines the relation between the parallel patterns of transient ischemia and the catastrophic events of myocardial infarction and sudden death.

Although studies of the triggering of transient ischemia are more advanced than are studies of triggering of infarction and sudden cardiac death, the available information does not explain why a typical patient may experience transient ischemia every morning, but suffer infarction only once in a lifetime. It is likely that external triggers, such as physical or emotional stress that cause transient ischemia, also cause infarction—but only in the presence of an additional relatively rare set of circumstances resulting in a vulnerable atherosclerotic plaque within a coronary artery.

PATHOLOGIC AND ANGIOGRAPHIC FINDINGS

Understanding the onset of occlusive coronary artery thrombosis—the cause of most cases of myocardial infarction and at least a third of the cases of sudden cardiac death—was greatly advanced in 1966 when Constantinides first reported that occlusive arterial thrombi were almost universally associated with fissures in atherosclerotic plaques.[11] In this supplement, Constantinides describes the animal research that led to his discovery in humans, and speculates on conditions that might predispose a plaque to rupture. A reproduction of a histologic section showing plaque rupture with thrombus formation is shown.

Identification of the presence of a fissure with an overlying thrombus does not reveal the mechanism of plaque rupture—specifically, a fixed specimen does not

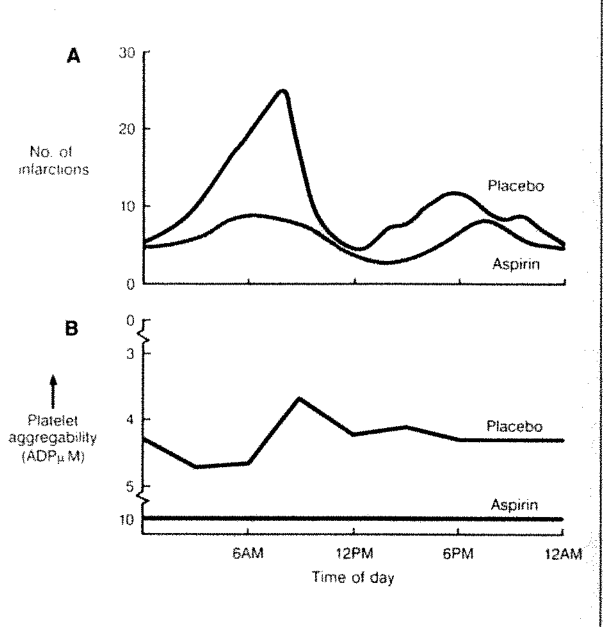

FIGURE 3. Prevention of morning myocardial infarction by prevention of platelet surge. Proprosed contribution of morning platelet surge to morning myocardial infarction and its prevention by aspirin. Illustration combines (*A*) the ability of aspirin to selectively reduce the morning peak in frequency of myocardial infarction (adapted from *Circulation*[14]); and (*B*) the ability of aspirin to abolish the morning increase in platelet aggregability. ADP = adenosine diphosphate. (Adapted from *N Engl J Med.*[13])

indicate whether the rupture occurred from the lumen into the plaque or from the plaque into the lumen. Barger and Beeuwkes describe a method for postmortem identification of the vasa vasorum of the coronary arteries and propose a mechanism whereby the pressure delivered to the plaque via the vasa vasorum may actually exceed that in the adjacent coronary artery lumen, thereby causing rupture of the plaque into the lumen.

The anatomic knowledge gained from these autopsy studies has been supplemented by angiographic studies in patients with myocardial infarction. Little reports that the atherosclerotic lesion causing the occlusive thrombus need not be severely stenotic before the event. In patients with mild to moderate coronary artery disease, the lumenal diameter narrowing measured on an angiogram obtained before the infarction was <50% in approximately 66% of cases. This finding is supported by measurements showing an average preexisting stenosis of only 56% in patients who have received thrombolytic therapy for myocardial infarction.[12] These findings indicate that thrombus formation rather than stenosing atherosclerosis is often the cause of disease onset, and suggest that efforts to prevent triggering of thrombosis could yield great clinical benefit.

PHYSIOLOGIC MECHANISMS

Substantial progress has been made in understanding the physiologic processes that might lead to onset of occlusive arterial thrombosis. In this supplement, Willerson and his colleagues summarize work they have been conducting since 1979 on the factors causing conversion of chronic to acute disease. Using a conscious, instrumented, dog model, they demonstrated that the cyclic flow reductions occurring after partial coronary artery occlusion are worsened by triggers such as low-level exercise, food and the presence of a person. Studies in patients with acute coronary syndromes, and in animals with experimental lesions, suggest that inhibition of platelet aggregation with thromboxane and serotonin antagonists might be an effective therapeutic option.

Recently, a cycle of information has been completed concerning the role of platelet aggregation in the onset of myocardial infarction. It was demonstrated in 1986 by Tofler et al[13] that platelet aggregability increases in the morning concurrent with the time of increased onset of infarction (Fig. 3A). Ridker et al[14] have subsequently analyzed the effect of aspirin on the time of day of onset of infarction in the Physicians' Health Study. In the placebo-treated group, there is a morning increase in infarction similar to that previously reported. In the aspirin-treated group, the morning peak was markedly reduced, as would be expected by elimination of the morning surge in platelet aggregability (Fig. 3B). The reduction in incidence of infarction by aspirin was 56% for the morning period versus only 32% for the remainder of the day.

Variations in fibrinolytic activity can also alter the likelihood of formation of occlusive thrombosis. In this supplement, Wiman and Hamsten report an extension of their earlier finding that plasminogen activator inhibitor excess is present in young patients with myocardial infarction. It has now been found that such an excess is also a marker for recurrent infarction.

The data on platelet aggregability and fibrinolytic activity illustrate a difference between acute intraindividual variations and chronic interindividual variations in processes likely to contribute to infarct onset. The Tofler-Ridker data demonstrate that surges in platelet aggregability within a patient in the morning increase the risk of infarct onset, and suggest that chronic interindividual variations (which are more extensive) are likely to be of importance. Conversely, the finding of Wiman and Hamsten demonstrates that chronic interindividual variations of plasminogen activator inhibitor alter the risk of infarct onset, and suggests that acute variations within a patient are also likely to be of importance.

RESULTS OF PHARMACOLOGIC INTERVENTION

The modes of action of the 3 types of pharmacologic agents that have been clearly documented to reduce the risk of myocardial infarction—aspirin, cholesterol-lowering agents and β-adrenergic blockers—can be examined in light of the new hypothesis of triggered onset. The role of aspirin in eliminating surges in platelet aggregability has been described. The recent demonstration by Brown et al[15] that reduction of cholesterol produced a greater

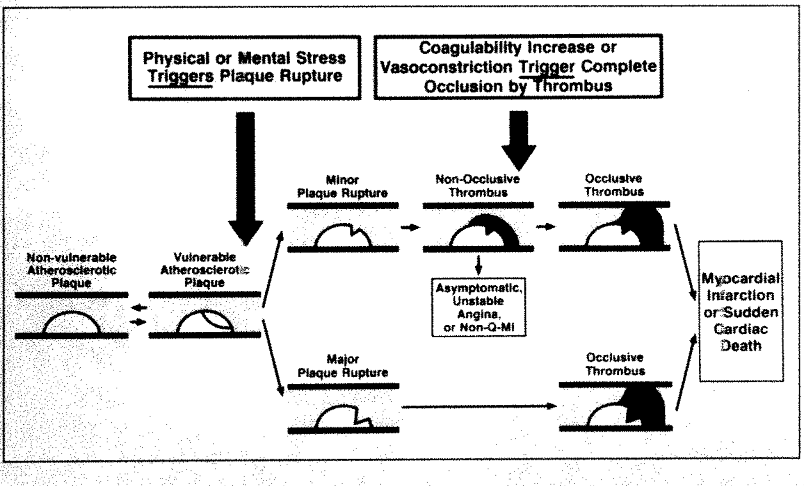
Physical or Mental Stress Triggers Plaque Rupture
Coagulability Increase or Vasoconstriction Trigger Complete Occlusion by Thrombus
Non-vulnerable Atherosclerotic Plaque
Vulnerable Atherosclerotic Plaque
Minor Plaque Rupture
Non-Occlusive Thrombus
Occlusive Thrombus
Asymptomatic, Unstable Angina, or Non-Q-MI
Major Plaque Rupture
Occlusive Thrombus
Myocardial Infarction or Sudden Cardiac Death

FIGURE 4. Triggering of coronary thrombosis. A hypothetical model by which daily activities may trigger coronary thrombosis. Three triggering mechanisms, (1) physical or mental stress producing hemodynamic changes leading to plaque rupture, (2) activities causing a coagulability increase and (3) stimuli leading to vasoconstriction, have been added to the well-known scheme depicting the role of coronary thrombosis in unstable angina, myocardial infarction (MI) and sudden cardiac death. See text for discussion. non-Q = non-Q-wave. (Adapted from *Circulation*.[16])

reduction in clinical events (including procedures) than in angiographically measured coronary stenoses, suggests that cholesterol lowering may reduce the vulnerability of plaques to rupture (perhaps by decreasing their lipid content), or may reduce events by decreasing platelet aggregability.

The data on the relation between prevention of infarction by β blockade and triggering are described in this supplement by Peters, Kostis, Goldstein, Frishman and Lazar. Peters analyzed the time of day of sudden cardiac death in the β-Blocker Heart Attack Trial (BHAT). Placebo-treated patients showed the previously reported morning increase in occurrence of death, while propranolol-treated patients appeared to be relatively protected in the morning. Kostis presents data indicating that the β blocker nadolol has a prolonged duration of action—a property of importance in providing 24-hour protection against ischemia. Goldstein presents an analysis of the overall results of the BHAT study and describes theories that have been tested to explain the ability of β-adrenergic–blocking agents to prevent infarction. In the final report of the supplement, Frishman and Lazar survey the numerous studies demonstrating a beneficial effect of β blockers, and propose a new hypothesis to explain their currently unexplained, but well-documented, cardioprotective effect.

GENERAL THEORY OF TRIGGERING OF CORONARY THROMBOSIS

The data presented in the supplement have led to formulation of a general hypothesis of the manner in which daily activities might trigger coronary thrombosis.[16] The hypothesis presented in Figure 4 adds the concept of triggering activities to the general scheme of the role of thrombosis in the acute coronary syndromes advanced by Davies and Thomas, Falk, Fuster, Willerson and others.[5,17–19]

It is proposed that the initial step in the process leading directly to coronary thrombosis is the development, with advancing age, of what can be termed a vulnerable atherosclerotic plaque. Plaque vulnerability is defined functionally as the susceptibility of a plaque to rupture. Development of such vulnerability is a poorly understood process, but is presumably a dynamic, potentially reversible disorder caused by changes in the constituents of the plaque, its blood supply via vasa vasorum, the functional integrity of the overlying endothelium, or a combination of these factors.

The theory that onset of thrombosis is unrelated to daily activities would presumably attribute disease onset solely to changes in the plaque, and the sequence would, therefore, lead directly from the plaque to occlusive coronary thrombosis without external modifiers. In the present formulation, however, it is proposed that onset might frequently begin when a physical or mental stress triggers a hemodynamic change sufficient to rupture a vulnerable plaque. (If such a trigger does not occur during vulnerability, the plaque may change with time and lose its vulnerability.) The rupture in the plaque may be major or minor, depending on factors such as the amount and type of collagen exposed.[20] A major plaque rupture produces a thrombogenic focus sufficiently intense to cause occlusive coronary thrombosis leading directly to myocardial infarction or sudden cardiac death. A minor rupture leads only to a mural thrombus that fails to produce symptoms, or leads to unstable angina or non-Q-wave myocardial infarction. Again, at this point external activities may lead to occlusion of the lumen. For example, a coagulability increase may trigger growth of the thrombus, or vasoconstriction may lead to complete occlusion of an already compromised lumen, leading to infarction or sudden death. Since normal individuals and even patients with coronary artery disease are constantly exposed to potentially triggering activities that do not produce coronary thrombosis, it seems likely that development of plaque vulnerability is the rarest event in this chain of causation.

It is likely that there is an inverse relation between the degree of plaque vulnerability and the intensity of the triggering stimulus required to produce rupture. For instance, an elderly patient with a severe fixed stenosis in a coronary artery and an extremely vulnerable plaque may develop thrombosis with only a minor stress, while a young patient with only a luminal irregularity might require a major stress (such as heavy lifting producing markedly increased arterial pressure) to trigger plaque rupture and coronary thrombosis. Sumiyoshi et al[21] reported that younger patients were more likely than older patients to report unusual stress before onset, but control data on the relative frequency of unusual stress in older versus younger patients are not available.

Various mixtures of triggering mechanisms may account for thrombosis. For example, the combination of physical exertion (producing a minor plaque rupture) followed by cigarette smoking (producing an increase in coronary artery vasoconstriction and a relatively hypercoagulable state) may be needed to cause disease onset. Thus, the onset of infarction, in some cases, may be the result of the unfortunate simultaneous occurrence of several events, each by itself of little consequence but catastrophic when occurring together.

SIGNIFICANCE

The primary immediate value of recognition of the circadian variation of acute onset of myocardial infarction is the emphasis that can be placed on pharmacologic protection during the morning hours for patients already receiving antiischemic and antihypertensive therapy. Although no scientific studies have been performed to test the hypothesis, it seems reasonable that long-acting antiischemic agents would have an advantage over short-acting agents in providing protection against myocardial infarction in the morning when the effects of short-acting agents taken the night before may attenuate.

The finding that infarcts appear to be triggered in the morning raises questions about the desirability of exercise in the morning. At present, the evidence that exercise is beneficial in reducing the risk of infarction is substantial,[22] and although theoretical concerns can be raised, there is no evidence that exercise in the morning is more hazardous than exercise at other times of the day. A controlled trial of thousands of individuals randomized to exercise in the morning or the evening would be needed to resolve the issue.

Even complete elimination of the morning increase in onset of myocardial infarction by optimal timing of exercise (if needed) and effective therapy would prevent only a small fraction of the total morbidity and mortality caused by this disorder. Although the incidence of disease onset is greatest in the 6 A.M. to noon period, the majority of infarcts occur at other times of the day, and their prevention requires a broader approach. For this reason, the primary significance of the recognition of circadian variation of disease onset is the support it provides for the broader concept that the onset of infarction at any time of the day is frequently triggered by activities of the patient. This concept provides a number of clues to the mechanisms of disease onset—clues that suggest the value of studies ranging from the epidemiologic to the molecular level.

It is hoped that the summary of this field of study provided by this supplement will lead other investigators to turn their attention to the numerous unresolved issues presented. A more complete understanding of triggering mechanisms should permit progress in the prevention of myocardial infarction. The means of prevention would not be to eliminate potential triggering activities—an undesirable and unattainable goal—but to design regimens that can be evaluated in randomized studies for their ability to sever the linkage between a potential triggering activity and disease onset.

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Subgroups of Patients with Atypical Circadian Patterns of Symptom Onset in Acute Myocardial Infarction

Elizabeth A. Gilpin, MS, Åke Hjalmarson, MD, and John Ross, Jr., MD

Circadian variation of onset of acute myocardial infarction has been noted in many studies and may carry important implications. However, only a few previous studies have attempted subgroup analysis. In 4,796 patients with documented acute myocardial infarction, the time of symptom onset was recorded. As in other studies, a peak occurred in the morning hours from 6 A.M. to noon with 28% of the population (1.16 times the average percent for the other time periods) experiencing symptom onset in that period ($p < 0.001$). There was a second lower peak (25%) in the evening hours between 6:01 P.M. and midnight, also observed in some previous studies.

Whether the presence of subgroups with specific clinical characteristics would exhibit different patterns and thereby contribute to these peaks in the overall population was then determined. In patients with a history of congestive heart failure ($n = 606$) or with non-Q-wave infarction ($n = 832$), a pronounced peak (29%) occurred only in the evening hours. In patients >70 years of age ($n = 1,422$), smokers ($n = 2,057$), diabetics ($n = 767$), women ($n = 1,213$) and patients taking β blocking drugs ($n = 847$), 2 nearly equal peaks were observed. Finally, in patients with previous myocardial infarction ($n = 1,104$), no peaks were observed. In a subgroup of patients ($n = 1,084$) free from the most important modifying factors, there was a single very pronounced late morning peak (32%), 1.39 times the average percent for the other time periods ($p < 0.001$), without evidence of a second evening peak. Marked differences in diurnal patterns of myocardial infarction onset occur in subgroups of patients with modifying factors, particularly non-Q-wave infarction, smoking, β blocker use, diabetes, prior congestive heart failure and prior myocardial infarction. The circadian pattern observed in a given total population reflects the contributions of these subgroups.

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A circadian variation in the frequency of onset of acute myocardial infarction (MI) has been described in a number of studies during the past 25 years.[1-8] Most show an increased onset in the morning hours with a peak incidence between 6 A.M. and noon, although a secondary peak in the late evening hours has also been reported.[1-3,5-7] We hypothesized that the pattern observed could be related to differences in the composition of the population with regard to subgroups of patients with various characteristics. Few studies of circadian rhythm have analyzed subsets of patients.[7,9] Therefore, the purpose of the present review, which is reported in detail elsewhere,[10] was to analyze in a large patient population the circadian patterns in the onset of symptoms of acute MI in various subgroups with characteristics considered to reflect or influence the physiologic status of the patient.

METHODS

Patients and variables: The date and time of symptom onset were recorded in 4,796 patients (25% women, mean age 63 ± 12 [mean ± standard deviation] years) who were later determined to have sustained a definite acute MI. The patients were part of a multicenter study supported by the Specialized Center of Research (SCOR) on Ischemic Heart Disease at the University of California, San Diego (UCSD Collaborative Database) in which data were collected prospectively to study the natural history of acute MI. The research nurses at all participating centers were trained to follow uniform protocols for patient entry and data gathering. One criterion for inclusion in the study was admission to the coronary care unit within 24 hours of symptom onset. Therefore, to verify eligibility, dates and times of onset of symptoms and coronary care unit admission were noted as precisely as possible. Further details regarding patient entry protocols and the variables studied have been described.[10]

In the present study, subgroups of patients were examined, based on the following variables: age, gender, history of congestive heart failure, history of previous MI, history of hypertension, history of diabetes, smoking at

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TABLE I Percentages of Patients With and Without Various Factors in the Four Six-Hour Intervals of Symptom Onset

	Time Interval			
	12:01 A.M.–6 A.M.	6:01 A.M.–Noon	12:01 P.M.–6 P.M.	6:01 P.M.–Midnight
Two peaks				
Age ≤70 years	22.7	(28.5)	23.9	24.9
Age >70 years	23.8	(26.7)	23.6	(25.9)
Sex (M/F)	23.0/23.1	(28.0)/(28.0)	24.4/22.2	24.6/(26.7)
Nonsmokers	23.4	(29.1)	23.8	24.2
Smokers	22.6	(26.5)	24.8	(26.2)
Nondiabetics	22.9	(28.0)	24.4	24.7
Diabetics	24.1	(27.5)	20.6	(27.8)
No β blockers	23.2	(28.4)	23.6	24.8
β blockers	21.8	(26.4)	24.9	(26.9)
One peak				
No Hx CHF	23.0	(28.5)	23.9	24.6
Hx CHF	22.9	24.8	23.4	(28.9)
Q-wave	23.3	(28.6)	23.8	24.3
Non-Q-wave	21.3	25.0	25.6	(28.1)
No peak				
No Hx prev MI	22.2	(28.7)	23.9	25.2
Hx prev MI	25.5	25.6	23.6	25.3
Typical pattern				
No Hx hypertension	24.3	(27.8)	23.2	24.6
Hx hypertension	21.3	(28.2)	24.7	25.8

Percentages in parentheses are peak periods of symptom onset.
CHF = congestive heart failure; Hx = history; MI = myocardial infarction; prev = previous.
(Adapted from *Circulation*.[10])

the time of study admission, use of β blockers before onset of symptoms and infarction type (Q-wave or non-Q-wave). For the population as a whole and for various subgroups, the frequency of symptom onset was tabulated for each hour in the day beginning 1 minute after the previous hour (i.e., 12:01 A.M. to 1 A.M., 1:01 A.M. to 2 A.M., etc.). In addition, 4 6-hour intervals were defined as follows: 12:01 A.M. to 6 A.M., 6:01 A.M. to noon, 12:01 P.M. to 6 P.M. and 6:01 P.M. to midnight.

Statistics: The distribution of symptom onset within the 4 time intervals was tested for uniformity in the overall population and in various patient subsets by the chi-square test for goodness-of-fit. The independence of time of onset from various factors was examined first with a chi-square statistic computed from a 2 × 4 (with and without the factor by the 4 time intervals) contingency table. Another test of such independence is the Mantel-Cox statistic from a "survival" analysis, in which the time of the event (onset of symptoms of MI) occurs within a 24-hour time interval. At the beginning of the interval no events have occurred and by the end of the interval each patient has had an event. Thus, the pattern of event times for patients with and without a given factor can be compared. Using a similar approach, factors univariately significant at the $p < 0.1$ level from this analysis were analyzed in a multivariate Cox regression to obtain some insight into which factors independently influence the pattern of events (time of onset).

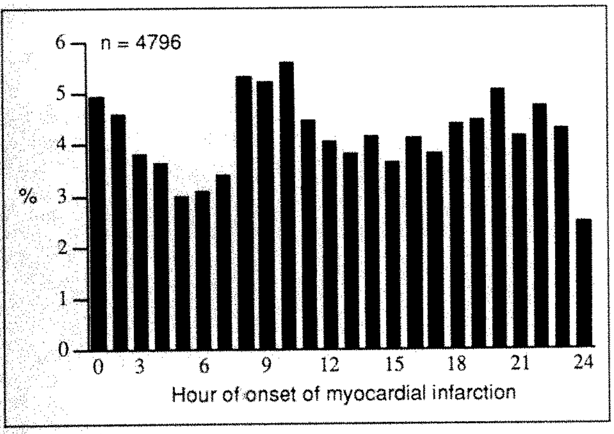

FIGURE 1. Distribution by hour of symptom onset of myocardial infarction for entire population. (Adapted from *Circulation*.[10])

For the entire population and certain subsets of patients, the ratios of the percentage for the highest peak to the average of the percentages for remaining periods were computed.

RESULTS

Entire population: The frequency of symptom onset is shown in Figure 1 for all 4,796 patients. The distribution is not uniform ($p < 0.001$) and exhibits a peak (28%) between the hours of 6:01 A.M. and noon. This peak was 1.16 times the average of the other 3 time periods. A secondary peak (25%) was discernible between the hours of 6:01 P.M. and midnight (Fig. 1).

Subgroups with both morning and evening peaks: Table I presents the percentages of patients—with and without various characteristics—with onset of symptoms in each of the 4 time intervals; percentages for the peak periods are in parentheses. Morning and evening peaks were the same size in patients >70 years of age, smokers, diabetics, those taking β blockers at time of onset and women.

Subgroups with dominant evening peak: In patients with a history of congestive heart failure, the evening peak was most pronounced, with 28.9% of this subgroup experiencing the onset of MI from 6:01 P.M. to midnight (Table I, Fig. 2), whereas the morning peak was attenuated (24.8%). Patients with non-Q-wave infarction exhibited only an evening peak (28.1%) with no morning peak (Table I, Fig. 2). The evening peak was even more marked (35.5%) in patients with a history of congestive heart failure in whom non-Q-wave infarction developed (Fig. 2).

Subgroup with no peak: Patients with a history of previous MI exhibited no discernible peak (Table I, Fig. 3). However, the circadian pattern in these patients appeared to be dependent on whether Q-wave or non-Q-wave infarction developed. In patients with previous infarction and present Q-wave infarction (Fig. 3), the incidence was highest from midnight to 6 A.M. and decreased

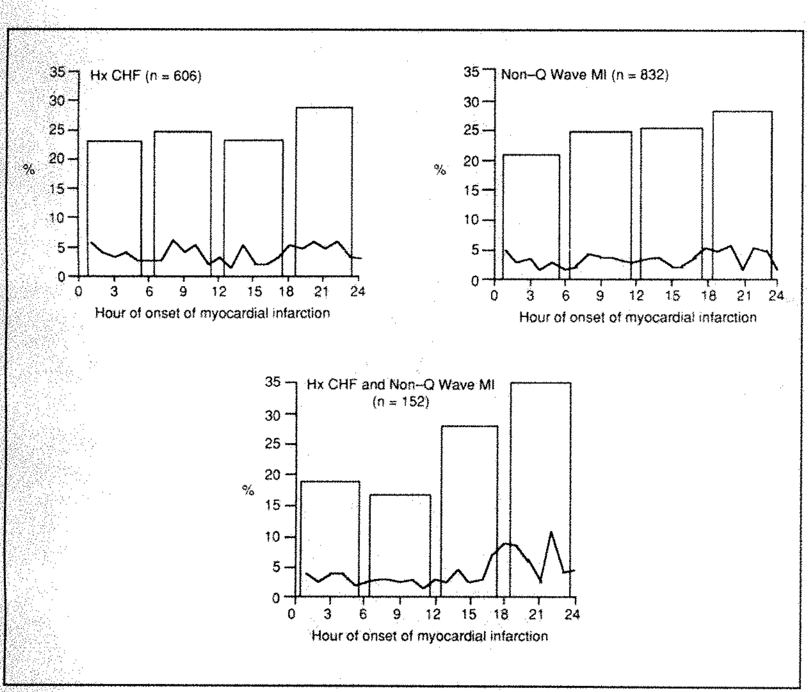

FIGURE 2. Distribution of hours of symptom onset of myocardial infarction by 6-hour intervals in subgroups with dominant evening peak (*bar graph*). *Bottom*, patients with a history of congestive heart failure who developed non-Q-wave infarction. The *line graph* shows the distribution by hour. CHF = congestive heart failure; Hx = history; MI = myocardial infarction. (Adapted from *Circulation*.[10])

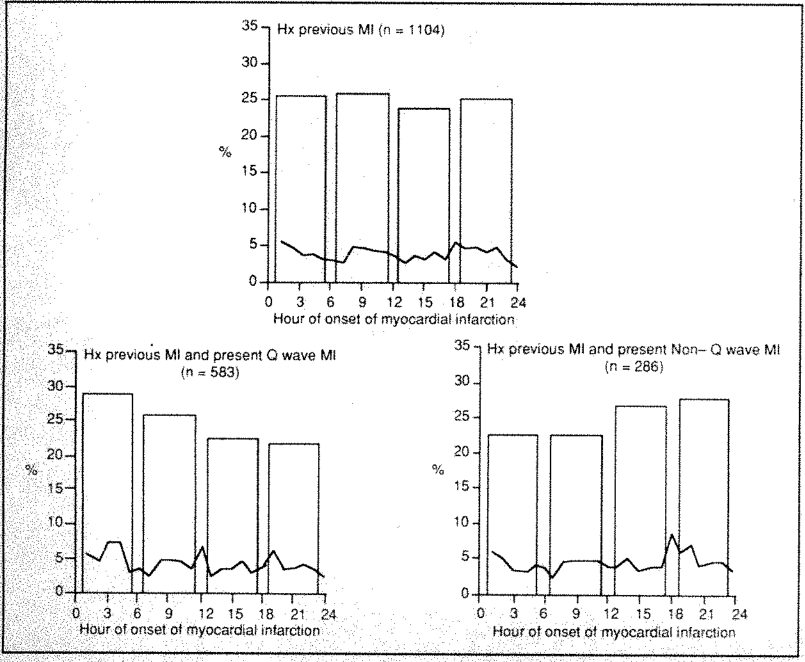

FIGURE 3. Distribution of hours of symptom onset of myocardial infarction by 6-hour intervals in patients with previous myocardial infarction (*bar graph*), and such patients with and without Q-wave myocardial infarction. The *line graph* shows the distribution by hour. Hx = history; MI = myocardial infarction. (Adapted from *Circulation*.[10])

throughout the day, whereas in patients with previous infarction and present non-Q-wave infarction (Fig. 3), the incidence of symptoms was lowest at that period and then increased.

Identification of modifying factors: The distribution of time of onset within the 4 intervals was not uniform for women, hypertensives, diabetics, smokers and patients with non-Q-wave infarction. Uniformity was also rejected ($p < 0.01$) for patients with a history of congestive heart failure and non-Q-wave infarction despite the small sample size, but could not be rejected for patients with a history of previous MI and present Q-wave or non-Q-wave infarction.

The hypothesis of independence (lack of interaction) for the time interval of symptom onset and the various factors could be rejected for history of previous MI, diabetics and patients with non-Q-wave infarction.

The pattern of actual infarct onset times differed for patients with a history of congestive heart failure, smokers, patients with non-Q-wave infarction and those taking β blockers at the time of infarction, compared to the subsets of patients without these factors. A multivariate Cox regression analysis of the factors identified non-Q-wave infarction ($p < 0.01$) and smoking ($p < 0.03$) as the most important determinants of time of symptom onset, with β blockade of marginal importance ($p < 0.1$).

Subgroup without various modifying factors: When the circadian pattern was examined for the subset of patients without 1 of the factors (Table I), only the single late-morning peak (Table I) was evident. The subgroup of patients 70 years of age or younger and not receiving β blockers (n = 2,777) showed 1 single, marked morning peak (29.4%) that was 1.25 times the average for the other 3 time periods, uniformity rejected ($p < 0.0001$). In a selected subgroup (n = 1,084) without the factors that showed either an interaction or a different pattern than for patients without the factor (i.e., those with Q-wave infarction without history of previous MI, congestive heart failure or diabetes who were not smokers or taking β blockers at the time of symptom onset), the morning period included 31.6% of all infarctions (Fig. 4, uniformity rejected, $p < 0.001$). The single peak was 1.39 times higher than the average of the other 3 time periods. This single pronounced peak was also observed for the 287 women (morning peak 30.2%) and for the 412 patients >70 years of age (morning peak 31.8%) within this subgroup.

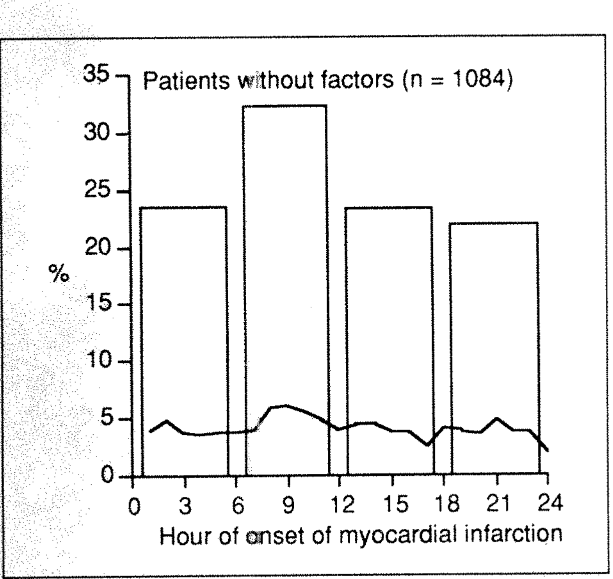

FIGURE 4. Distribution of hours of onset of myocardial infarction by 6-hour intervals in subgroups free from selected modifying factors (*bar graph*). The *line graph* shows the distribution by hour. (Adapted from *Circulation*.[10])

DISCUSSION

The present study confirms the finding of other studies,[1-8] that the incidence of symptom onset is most frequent in the late morning, from 6:01 A.M. to noon, and in our population as a whole there is also a second, smaller peak in the late evening, between 6:01 P.M. and midnight, also in accordance with some other studies.[1-3,5-8] Only recently has it been suggested that some subsets of patients with acute MI may not have the characteristic diurnal rhythm.[7,9,10]

Our finding of an evening peak in patients taking β blockers at the time of MI is in agreement with findings in the subgroup treated with β blockers in the Multicenter Investigation of the Limitation of Infarct Size (MILIS) reported by Muller et al.[7] However, patients receiving β blockers in the present study (n = 847) showed a reduced late-morning peak and an equal late-evening peak, whereas in the MILIS population patients receiving β blockers (n = 135) had the highest incidence of infarction onset in the late evening, but the adjacent early-morning peak (midnight to 6 A.M.) was nearly as high.[7] In a recent preliminary report from the Diltiazem Reinfarction Study,[8] in patients with non-Q-wave infarction (n = 540) and in the subgroup not receiving a β blocker (n = 397), the incidence of infarction was higher during the last 2 quarters of the day (each 27%) than in the first 2 quarters (21 and 24%), a pattern consistent with the subset (n = 832) in our population with non-Q-wave infarction. Our findings of an altered circadian pattern for patients over age 70, women, those with a previous MI and smokers are at odds with the results reported in the MILIS study; however, their population was age-limited and the subgroups analyzed were small. The findings of 2 peaks (morning and evening) for patients with diabetes, and only 1 evening peak for patients with a history of congestive heart failure, and that patients with a history of hypertension exhibit the typical circadian pattern, require confirmation in further studies.

Circadian patterns in selected populations: The restriction of patients included in various reported studies may explain some of the differences in the observed patterns of circadian variation. The 2 studies reporting a single peak in an entire population were in highly selected patient populations.[4,8] The World Health Organization reported on 8,900 patients from 19 European countries. These patients were under 65 years of age and admitted before 1976, before the widespread use of β blockers.[4] A similar subset of our population also exhibited only 1 morning peak. However, some of the individual centers within this study did report a second evening peak, while others reported none. These differences could be due to small sample sizes, different customs in the countries regarding the evening meal or a different distribution of patients with modifying factors. Interestingly, centers with an older age distribution or more diabetics tended to show the second evening peak. In the Multicenter Chest Pain study,[8] the mean age was 58 years (compared to 65 years in our population) and only a single late-morning peak was found. The patients in the MILIS study[7] were all younger than 75 years of age, and among the subset with no prior β blockade ($n = 711$) there appeared to be only a single peak between 6 A.M. and noon. Our results indicate that it was probably not age that caused the alteration of the circadian pattern, but rather the presence of other factors that are more prevalent among older patients.

Implications: Certain factors appear to modify the characteristic circadian variation of infarction onset and predispose persons with those factors to experience onset of infarction later in the day rather than in the morning (6 A.M. to noon). The second peak seen in our total population appeared to reflect the presence of these persons. Thus, populations or subgroups free from these modifying factors have only 1 distinct morning peak. Since different times of onset may reflect pathophysiologically different mechanisms, subgroup analysis appears important for establishing such patterns. Therefore, future analyses of diurnal rhythms concerned with physical and mental stress, hemodynamic variations, neuroendocrine responses and thrombotic or fibrinolytic activities seem most likely to provide further information about the pathogenesis of MI onset when carried out in well-defined subgroups of patients of adequate size.

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Beta Blockers and the Primary Prevention of Nonfatal Myocardial Infarction in Patients with High Blood Pressure

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A population-based, case-control study was conducted to determine whether β blockers, used for the treatment of high blood pressure, prevent first events of coronary heart disease. All study subjects were health-maintenance organization enrollees with pharmacologically treated hypertension. Patients presented in 1982 to 1984 with new coronary heart disease, and control subjects were a probability sample of eligible hypertensive enrollees free of coronary heart disease. With the investigators blind to case-control status, the subjects' medical records were reviewed for other coronary risk factors, and the health-maintenance organization's computerized pharmacy database was used to ascertain the use of β blockers. A larger proportion of controls than cases were using β blockers. This difference was confined to the subgroup with nonfatal myocardial infarctions. For current use, the estimated relative risk for nonfatal myocardial infarction was 0.62 (95% confidence interval, 0.39 to 0.99). Among current users of β blockers, higher doses conferred greater protection. Past use and total lifetime intake of β blockers were only weakly associated with case-control status. The current use of β blockers may prevent first events of nonfatal myocardial infarction in patients with high blood pressure.

(Am J Cardiol 1990;66:12G–14G)

In a meta-analysis of 9 randomized trials of the treatment of high blood pressure, MacMahon et al[1] reported a reduction of 39% in the incidence of fatal and nonfatal stroke. For coronary heart disease, on the other hand, the treatment of high blood pressure decreased the incidence of fatal and nonfatal events by only 6 and 8%, respectively. Thus, although coronary heart disease is the most common complication of untreated high blood pressure, the pharmacologic treatment of hypertension has had little effect in reducing the incidence of coronary artery disease. The trials included in this meta-analysis generally used a thiazide-like diuretic. In the last few years, the Medical Research Council and the International Prospective Primary Prevention Study in Hypertension trials have reported a reduction of coronary heart disease in selected subgroups.[2,3] The Metoprolol Atherosclerosis Prevention in Hypertensives Study has reported a decrease in fatal coronary events in patients treated with metoprolol, although controversy about the relation of this study to the Heart Attack Primary Prevention in Hypertensives Study persists.[4,5]

METHODS

The methods of the case-control study used in the current study have previously been described in detail.[6] Briefly, the setting was the Group Health Cooperative of Puget Sound (GHC), a health-maintenance organization with over a third of a million members. To be eligible, subjects had to be enrolled in the GHC during 1982 to 1984 and aged 30 to 79 years. Patients were all such enrollees who had physician-diagnosed high blood pressure and who presented with an incident event of coronary artery disease, either angina or myocardial infarction. We identified potential cases from hospital records and from the death-registry files of Washington State. Controls also had physician-diagnosed high blood pressure, and they had no prior coronary artery disease. To identify potential controls, we used the computerized pharmacy database, which included a record of all prescriptions filled by enrollees at GHC pharmacies. Selecting as potential controls those patients who received medicines that may be used to treat high blood pressure, we frequency-matched the controls to the cases by age, gender and year of presentation at a ratio of 3:1. For each case and control, we reviewed the outpatient medical record to determine eligibility and to gather information about blood pressure, cholesterol, smoking status and other known risk factors for coronary artery disease. For hospitalized cases, we reviewed the inpatient medical re-

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TABLE I Estimated Relative Risk of Nonfatal Myocardial Infarction Associated with the Use of Beta Blockers

				Initial		Adjusted	
Use	Reference	Cases	Controls	RR	95% CI	RR	95% CI
Current	Past or never use	126	737	0.62	0.40–0.99	0.62	0.38–1.02
Current	Never use	104	656	0.68	0.41–1.11	0.67	0.39–1.13
Past	Never use	98	468	1.53	0.89–2.63	1.32	0.72–2.41
Ever	Never use	126	737	0.93	0.62–1.39	0.89	0.58–1.38

The initial estimate is adjusted only for the number of days on which a patient filled a prescription for an antihypertensive medicine during the year before the index date. The adjusted estimate is adjusted additionally for the following covariates as well: age, sex, year of presentation, systolic blood pressure, smoking status, cholesterol level, family history, physical activity, number of physician visits during the year before the index date, duration of treated hypertension, length of time in Group Health Cooperative and the presence of diabetes mellitus, congestive heart failure and cerebrovascular disease. Cases and controls indicate the number of subjects who entered each analysis.

CI = confidence interval; RR = estimated relative risk.

TABLE II Estimated Relative Risk of Nonfatal Myocardial Infarction Associated with Current Dose and Lifetime Intake of Beta Blockers

	Initial		Adjusted	
Type of Dose	RR	95% CI	RR	95% CI
Current dose*				
<160 mg/day	0.66	0.41–1.08	0.67	0.40–1.13
≥160 mg/day	0.40	0.12–1.34	0.39	0.11–1.37
P value for trend†		0.028		0.038
Lifetime intake*				
<172,800 mg	0.91	0.60–1.39	0.87	0.55–1.37
≥172,800 mg	1.04	0.46–2.34	1.02	0.43–2.42
P value for trend		0.832		0.723

* The dose is expressed as the physiologic equivalent in mg of propranolol hydrochloride. For current dose, the reference group includes past users and never users. A lifetime intake of 172,800 mg is the equivalent of about 160 mg/day for 3 years. For lifetime intake, the reference group is never users.

† Using logistic regression, we calculated the p value for the test for trend by the likelihood-ratio method. The initial and adjusted estimates are as defined in Table I.

Abbreviations as in Table I.

cord to validate the diagnosis of myocardial infarction. We determined the use of β blockers according to the information available in the GHC computerized pharmacy database.

The primary hypothesis involved the "current" use of β blockers. For cases, we ascertained their use at the time of their index event. For controls, we assessed their use of β blockers at a computer-generated random date chosen from the same distribution of dates as those of the patients. The dose of β blockers was expressed as the physiologic equivalent in milligrams of propranolol hydrochloride. The GHC pharmacy database comprises a list of prescriptions rather than individuals. The longer the prescription for a certain drug lasts, the fewer visits a patient makes. Each control's probability of being sampled from the pharmacy database depended on the frequency of pharmacy visits. This differential probability of selection is a well-recognized consequence of sampling on visits.[7] Among the available methods of adjustment, we chose to treat the frequency of pharmacy visits as a covariate in the multivariable models. All results presented here include estimates adjusted for this visit-based sampling. In the analysis, we used logistic regression.[8]

RESULTS

The frequency matching produced cases and controls with comparable distributions of age, sex and index dates. For the 126 cases with nonfatal myocardial infarction, the mean untreated blood pressure was 168/104 mm Hg; and for the 737 controls, it was 166/104 mm Hg. The average most recent blood pressure was 146/86 mm Hg for the cases, and 143/86 mm Hg for the controls. Cases and controls were receiving pharmacologic therapy for high blood pressure for an average of 7.3 and 7.6 years, respectively. Our data confirmed traditional risk factors for coronary disease, such as smoking and high cholesterol level.

Table I summarizes the primary results of the study for patients with nonfatal myocardial infarction. As previously reported,[6] the estimated relative risk of nonfatal infarction associated with the current use of β blockers was 0.62 compared with past or never use. This estimated relative risk is equivalent to a 38% reduction in the incidence of nonfatal myocardial infarction. Past use of β blockers was associated with a slight increase in the relative risk of nonfatal myocardial infarction, but the 95% confidence interval was wide and included 1.0. Use at any time, which included both current and past use, was only weakly associated with case-control status (0.89 with 95% confidence interval of 0.58 to 1.38). The choice of the reference group—either never users or the combination of never users and past users—had little effect on the point estimate of the effect of the current use of β blockers: both estimates of the relative risk (0.62 and 0.67) suggest that β blockers reduced the incidence of nonfatal myocardial infarction.

Table II summarizes the effect of the dose of β blocker on the estimated relative risk of nonfatal myocardial infarction. All doses are expressed as the equivalent in milligrams of propranolol. Current dose refers to the dose taken at the index date, and lifetime intake is the sum of all doses dispensed by GHC pharmacies between 1977 and the index date for each subject in the study. As previously reported,[6] the dose-response relation for the current dose is unlikely to be the result of chance alone ($p = 0.028$). This is so even after adjustment for potential confounders ($p = 0.038$). In Table II, we also report the effect of lifetime intake of β blockers. Defined as more than the equivalent of 160 mg of propranolol/day for 3 years, high lifetime intake was only weakly associated with case-control status, and there was no statistically significant dose-response relation either before or after adjustment for potential confounders. Defining the cutoff point for low and high lifetime intake as 116,800 and 233,600 mg (the equivalent 160 mg of a β blocker/day for 2 and 4 years, respectively) affected the results in only trivial ways. Neither lifetime intake as a continuous variable nor the duration of β-blocker use was associated with case-control status.

DISCUSSION

Data from our case-control study suggested that β blockers may reduce the incidence of nonfatal myocardial infarction in patients with high blood pressure. There was no apparent benefit for the outcomes of angina pectoris or fatal myocardial infarction.[6] In the subgroup with nonfatal myocardial infarction, the current use of β blockers appeared to be protective, and the estimated effect was influenced little by the choice of the reference group (Table I). Moreover, the current use of high doses of a β blocker conferred greater protection than the current use of low doses of a β blocker. In contrast, various measures of a lifetime intake were only weakly associated with case-control status.

These findings are useful for suggesting potential mechanisms of action. Since β blockers did not prevent fatal events in this study, our data provide little or no evidence for an antiarrhythmic mechanism. With the small numbers of fatal events, we did not have much power to detect a protective effect in this subgroup if it were present. While a dose-response relation with lifetime intake would have been consistent with an antiatherosclerotic mechanism, such an association was not present in this study. In contrast, current use was important, and the higher the dose, the greater the protection. This finding suggests the need for adequate blood levels, and it is consistent with several possible mechanisms, including the well-known antianginal properties of β blockers as well as their possible, but controversial, antiplatelet properties.[9] Interestingly, Muller, Tofler and Stone have recently suggested that the onset of nonfatal myocardial infarction may be triggered by external events causing rupture of atherosclerotic plaques.[10] The interruption of the consequences of an external trigger are also likely to be associated with the current use of β blockers in a dose-response fashion.

The results of our study, a case-control study rather than a randomized trial, must be interpreted with caution. We can suggest several alternative explanations for our findings. First, we cannot entirely exclude the role of chance. Second, we used data on coronary risk factors available in the medical record, and there may be other unmeasured or unknown confounders. Third, from other studies we know that the prognosis of compliant patients is better than that of noncompliant patients,[11] and our method of sampling control subjects may have selected more compliant patients. Finally, we sampled controls from the pharmacy database, and they may also be more likely to take over-the-counter medicines such as aspirin. While we cannot exclude these alternative explanations, our data suggest that β blockers prevented nonfatal infarctions in patients with high blood pressure. These findings need to be confirmed in other studies.

In summary, we have used the case-control method, which is a statistically efficient design, to estimate therapeutic efficacy. With the many new classes of agents available to treat high blood pressure—α blockers, calcium antagonists and angiotensin-converting enzyme inhibitors—we are unlikely to have evidence of their efficacy against major disease end points from randomized trials for many years, if at all. We anticipate a new generation of population-based, case-control studies that compare these major classes of antihypertensive agents in terms of their ability to prevent cardiovascular disease in patients with high blood pressure.

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Epidemiologic Studies Demonstrating Increased Morning Incidence of Sudden Cardiac Death

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To determine if sudden cardiac death shows a circadian variation, the mortality records of the Massachusetts population and the Framingham Heart Study were analyzed. The Massachusetts mortality data analysis revealed an increased morning incidence for out-of-hospital cardiac deaths similar to that previously described for nonfatal myocardial infarction. The records of the Framingham Heart Study allowed more comprehensive analysis of the time of sudden cardiac death. In this study, a prominent circadian variation was also identified in which frequency of sudden cardiac death increased sharply between 6 A.M. and 9 P.M.; distribution was fairly even throughout the rest of the day. This circadian pattern may be explained in part by physiologic changes that increase the likelihood of ventricular fibrillation or increase the risk of thrombosis in the morning hours. The possible role of the morning increase in physical and mental activity as a trigger of sudden cardiac death requires further investigation.

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The recent finding of an increased likelihood of nonfatal myocardial infarction during the late morning[1-3] stimulated investigation to determine whether a similar circadian pattern existed for sudden cardiac death. This disorder accounts for approximately 15% of deaths in industrialized societies and is closely related to the problem of nonfatal myocardial infarction. Investigation of time of sudden cardiac death is complicated by several obstacles. Diagnosis of sudden cardiac death can rarely be confirmed by objective evidence. Time of death cannot always be determined because many deaths are unwitnessed and, since the victims die, the possibility of obtaining firsthand historical data is eliminated. Furthermore, since the likelihood that sudden cardiac death will be unwitnessed is higher during the night than during other times of day, many deaths occurring during the night may escape analysis, thereby creating an artificially low frequency of events during the night. Finally, it is generally believed that approximately one third of sudden cardiac deaths are associated with acute myocardial infarction.[4] Since the incidence of nonfatal myocardial infarction shows a circadian variation, this association complicates the assessment of the circadian pattern of those sudden cardiac deaths not secondary to acute myocardial infarction.

MASSACHUSETTS MORTALITY DATA STUDY

The mortality records of the Massachusetts population were evaluated in collaboration with the Massachusetts Department of Public Health to determine time of occurrence of sudden cardiac death in a large cohort.[5] In 1983, 26,798 deaths in Massachusetts occurred due to disease of the circulatory system (49% of total deaths). Since sudden cardiac death is not uniformly coded in the International Classification of Disease system, it was defined as death from cardiac disease occurring within 1 hour after onset of symptoms. Based on retrospective review and evaluation of death certificates, 2,203 individuals were identified who met the study definition of sudden cardiac death.[5]

The time of day of death in this population showed a circadian variation with a primary peak in the late morning (from 9 to 11 A.M.) and a minor secondary peak in the afternoon (Fig. 1). This circadian variation was statistically significant ($p < 0.01$) by applying chi-square tests for goodness of fit and 1- and 2-harmonic regression models. There was a strong similarity between the circadian variation of sudden cardiac death and the circadian variation previously described for nonfatal myocardial infarction.[1]

An increased morning incidence was also demonstrated for out-of-hospital cardiac deaths (as opposed to

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sudden cardiac deaths); in-hospital cardiac deaths were approximately evenly distributed over a 24-hour period.[5] Since it is likely that normal endogenous and exogenous circadian rhythms are altered in hospitalized patients, one may conclude that usual (out-of-hospital) sleep/activity patterns are at least in part responsible for the increased morning incidence of sudden cardiac death.

SUDDEN CARDIAC DEATH IN THE FRAMINGHAM HEART STUDY

The Massachusetts Death Record Study was based solely on death certificates, which have certain limitations. Therefore, an analysis of time of sudden cardiac death was performed in collaboration with the Framingham Heart Study, which provided major methodologic advantages.[6] Briefly, in 1948 the Framingham Heart Study originally included, 5,209 residents of Framingham, Massachusetts, ages 30 to 62. All data concerning the death of an individual of this population have been routinely supplied to the Mortality Review Committee of the Framingham Heart Study, which determines the underlying cause of death. For the purposes of a circadian analysis, the mortality charts of the Framingham Heart Study population were reviewed to identify all cases of sudden cardiac death and to determine time of death. Definite sudden cardiac death was defined as out-of-hospital death occurring within 1 hour from onset of symptoms in an apparently healthy subject, if cause of death could not be reasonably attributed on the basis of full clinical information to a disease other than coronary artery disease. To permit inclusion of unwitnessed deaths, possible sudden cardiac deaths were defined as deaths that may have occurred within 1 hour after onset of symptoms and in which there was no apparent noncardiac cause of death. The time of death was determined on the basis of information from the highest ranked of the following sources: (1) interviews with witnesses of the death, (2) medical reports, (3) newspaper accounts and (4) death certificates.

At the time of analysis, a total of 2,458 individuals of the original cohort of the Framingham Heart Study had died (47%). We identified 264 definite sudden cardiac deaths (11% of total deaths) and 165 possible sudden cardiac deaths (7% of total deaths). The precise time of death could be identified for 59% of all (definite or possible) sudden cardiac deaths. The time of unwitnessed deaths was estimated on the basis of the most precise information available. For example, when an individual was found dead in bed, the probability of death was evenly distributed between midnight and 6 A.M. If no estimate of time of death could be made, the probability of death was evenly distributed over 24 hours. Assumptions were made in a manner to decrease the likelihood of detection of morning increase in sudden cardiac death.

Time of day of definite sudden cardiac death showed a prominent circadian variation with a low frequency during the night and a morning peak, as would be expected from the requirement that the deaths be witnessed. However, a significant circadian variation remained when the possible sudden cardiac deaths were added to the analysis (Fig. 2). There was a sharp increase in frequency of sudden cardiac death from 6 to 9 A.M., followed by an almost equal distribution of sudden cardiac deaths during the other times of day. This circadian variation of sudden cardiac deaths was similar for men, women, older and younger patients.

STUDIES ON ACTIVITY BEFORE SUDDEN CARDIAC DEATH

Several studies investigated the relation between activity level and incidence of sudden death. Myers and Dewar reported that the level of arousal and activity was positively correlated with the incidence of sudden arrhythmic death.[7] Other investigators reported that the incidence of sudden death during sleep was significantly below the expected incidence if occurrence of sudden cardiac death was randomly distributed throughout a 24-hour period.[8] Furthermore, in an investigation of young soldiers during World War II, sudden death from obscure causes occurred in many cases in association with strenuous exertion, indicating that the activity level may be associated with increased risk of sudden death.[9]

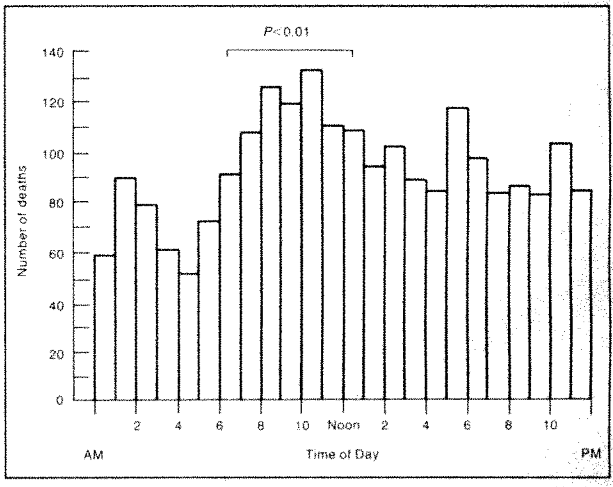

FIGURE 1. Time of day of death of 2,203 patients who died of sudden cardiac death in Massachusetts in 1983. (Adapted from *Circulation*.[5])

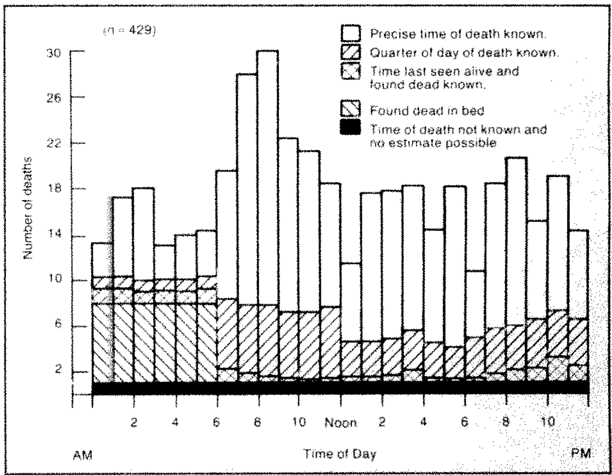

FIGURE 2. Time of day of all 429 definite or possible sudden cardiac deaths that have occurred in Framingham Heart Study population. (Adapted from *Am J Cardiol*.[6])

CONCLUSIONS

The reviewed data indicate a circadian variation in the incidence of sudden cardiac death with a significantly increased morning incidence, and suggest that the increased physical and mental activity that usually occurs during the morning may, at least in part, be responsible for the pattern. The observation that sudden cardiac death is more likely to occur during the morning is compatible with leading theories that sudden cardiac death may either be a consequence of myocardial ischemia,[10] evidenced by pathologic findings of coronary thrombi, or may be the result of a primary arrhythmic event.[11] Both mechanisms are more likely to occur during the morning, since this is a time of increased systemic arterial blood pressure and platelet aggregability together with reduced fibrinolytic activity.[12] The increased catecholamine levels also present may reduce the threshold for ventricular fibrillation.[13]

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Timing and Triggers of Transient Myocardial Ischemia

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Use of exercise tolerance testing and new techniques of ambulatory electrocardiographic monitoring to more objectively measure myocardial ischemia have enabled clinicians to better recognize the magnitude, timing and variable characteristics of transient ischemic events. These commonly occurring events in patients with coronary artery disease have a diurnal pattern strikingly similar to that reported for catastrophic cardiovascular events such as myocardial infarction, sudden cardiac death and stroke. Whether those factors that contribute to reversible ischemic events are similar to those causing infarction and sudden death has not been resolved. However, the parallel increase in morning activity for these related phenomena suggests that a better understanding of the triggers of reversible myocardial ischemia may help improve understanding of the causes of myocardial infarction and sudden cardiac death.

(Am J Cardiol 1990;66:18G–21G)

Graded exercise tolerance testing has been useful in characterizing differences in the thresholds for the development of ST-segment depression or angina during different times of the day. Henkels et al,[1] studying patients with stable coronary artery disease who discontinued antiischemic therapy, demonstrated that the time to development of ST-segment depression or angina during graded exercise was shortest in the morning, compared to other times of the day. Yasue and colleagues,[2] studying patients with variant angina, noted that subjects were more likely to develop typical ST elevation and symptoms in the morning, compared to the afternoon, even though these patients were able to exercise for longer durations in the afternoon. Other studies have suggested that there is no diurnal variation in ischemic threshold measured during exercise testing in the morning compared to the afternoon.[3] However, it is important to note that in some studies, exercise responses were compared while a large percentage of patients were taking antiischemic medication. Recent studies suggest that standard antianginal medication may significantly alter this diurnal pattern.[4-6]

TIMING OF TRANSIENT MYOCARDIAL ISCHEMIA

Improved techniques of ambulatory electrocardiographic monitoring have enabled us to record the frequency, timing and characteristics of transient ischemia occurring during routine out-of-hospital activity in patients with stable coronary disease. Such studies have demonstrated that episodes of ischemia during routine activity are frequent, typically asymptomatic and often initiated at low heart rates.[7-9] The peak frequency and duration of transient ischemia has been shown to occur consistently in the morning hours between 6 A.M. and noon (Fig. 1).[4-6,10] In addition, we have shown that when the timing of ischemic episodes is adjusted for variable wake time, the greatest frequency of events is seen in the first few hours after awakening (Fig. 1).[10] This indicates that the morning increase in ischemia is more dependent on factors associated with the sleep/wake cycle or activities associated with morning arousal than with the absolute time of day.

POTENTIAL TRIGGERS OF TRANSIENT MYOCARDIAL ISCHEMIA

Attempts have been made to better understand those factors that precede discrete episodes of ischemia or have temporal patterns that mimic those of ischemic episodes.

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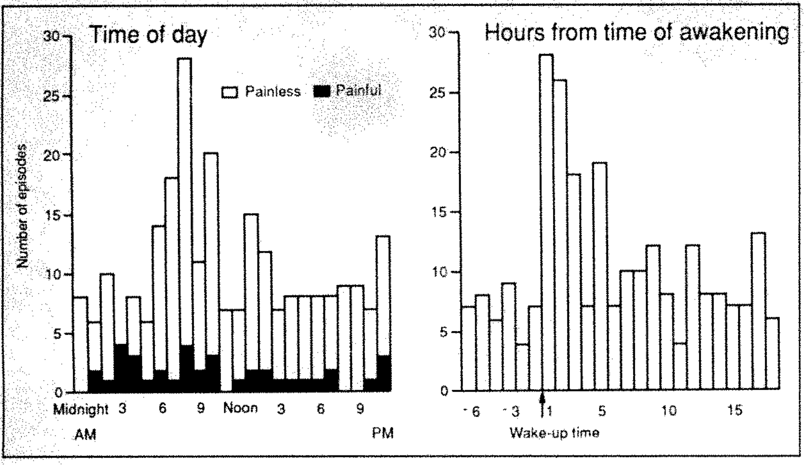


FIGURE 1. The hourly distribution of the number of episodes of ischemic ST-segment depression in 24 patients with coronary artery disease undergoing ambulatory monitoring while not taking antiischemic medication demonstrates an increased frequency in the morning hours between 6 A.M. and noon (*left*). When the number of hourly episodes is standardized according to time from waking, the peak frequency of ischemic episodes is noted to occur in the first few hours after waking (*right*). Physiologic patterns intrinsic to biologic systems, altered physiologic response related to the sleep/wake cycle or differences in extrinsic stimuli after waking may all contribute to this temporal pattern of transient myocardial ischemia. (Adapted from *Circulation*.[9])

An examination of these potential extrinsic and intrinsic triggers and physiologic events with similar timing may help us better understand the temporal distribution of ischemic activity. Barry et al[11] examined perceived physical activity and mental stress and its relation to transient ischemia recorded during ambulatory monitoring. The majority of episodes of transient myocardial ischemia were preceded by possible triggering events described by subjects as varying from usual activity to stressful physical or mental activity. When the duration of ischemia was normalized for the amount of time spent in each category of physical or mental activity, it was demonstrated that there was a much higher likelihood of ischemia occurring during those activities perceived as being most physically or mentally engaging (Fig. 2). The mechanism by which events may trigger reversible myocardial ischemia is likely multifactorial.

The relative contribution of decreases in myocardial oxygen supply versus increases of myocardial oxygen demand and their roles in producing myocardial ischemia have long been a subject of controversy. The precipitation of ischemia by increases in myocardial oxygen demand in the setting of significant obstructive coronary artery disease is well appreciated. Only recently have we obtained a better appreciation of provoked changes in coronary artery caliber and flow, and its possible role in producing myocardial ischemia. *In vitro* observations and animal studies have demonstrated an exaggerated or paradoxical vasoconstrictor response when damaged endothelium is exposed to substances such as histamine, serotonin or acetylcholine.[12,13] Unlike the vasodilation that is seen in normal human subjects during intracoronary infusion of acetylcholine, patients with minimally or severely diseased coronary arteries demonstrate paradoxical vasoconstriction to this stimulus.[14] Therefore, circulating products may induce unsuspected alterations in coronary artery tone and flow in the patient with diseased coronary arteries. Investigators using markers such as rubidium-82 (^{82}Rb) myocardial uptake during positron emission tomography and quantitative angiography have attempted to examine the effects of exertional and nonexertional tasks on coronary artery flow and myocardial perfusion. Deanfield and associates[15,16] have demonstrated a region-

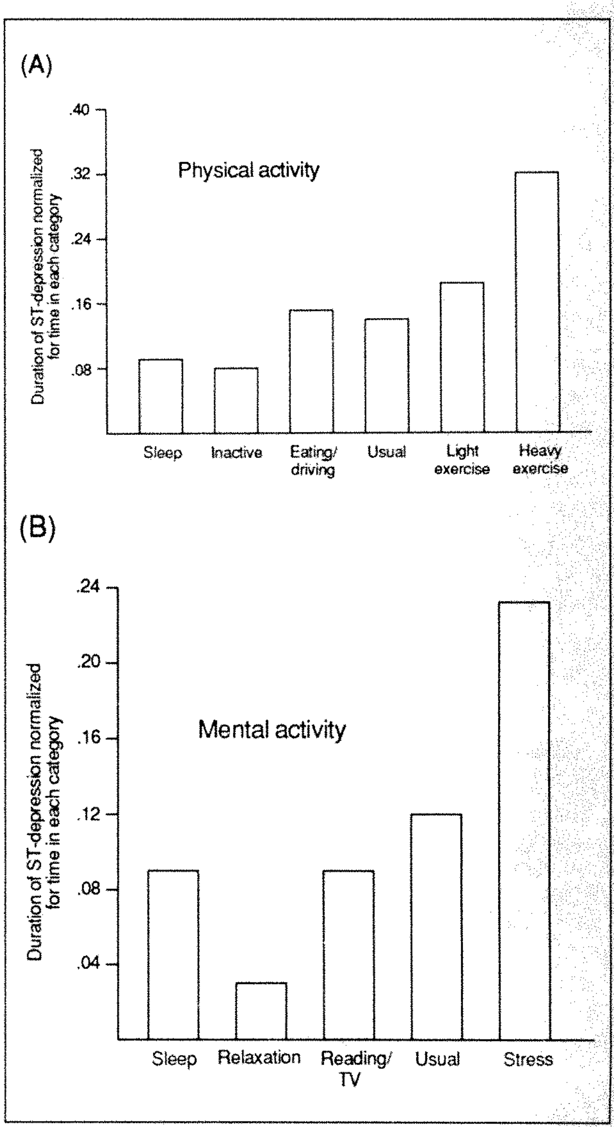


FIGURE 2. The duration of ST-segment depression observed during ambulatory monitoring is normalized for the total period of time spent in categories of increasing physical (*A*) and mental activity (*B*). More intense physical activities and more stressful mental activities were accompanied by significantly more ischemia/unit time. (Adapted from *J Am Coll Cardiol*.[17])

al reduction in myocardial perfusion (as demonstrated by decreased ^{82}Rb uptake) associated with the performance of mental arithmetic tasks or cold forearm ice water immersion. These reductions were qualitatively similar to regional reductions in uptake associated with supine exercise in the same patients. Interestingly, during the nonexercise tasks, the perfusion abnormalities were generally associated with smaller increases in heart rate and blood pressure than those associated with exercise. Similar characteristics were identified for spontaneous events of myocardial ischemia that occurred unassociated with task performance. In addition, the simple act of smoking a single cigarette has been shown to cause a decrease in ^{82}Rb uptake at lower levels of myocardial oxygen demand (as measured by heart rate and blood pressure response) than that needed to provoke ischemia with exercise.[17] In fact, ambulatory electrocardiographic monitoring studies have demonstrated a significantly greater frequency and duration of transient ischemia in current smokers with coronary disease when compared to matched samples of nonsmokers with coronary disease.[18] This further suggests that certain activities may precipitate vasoconstriction, impair coronary blood supply and be important in the onset of reversible myocardial ischemia.

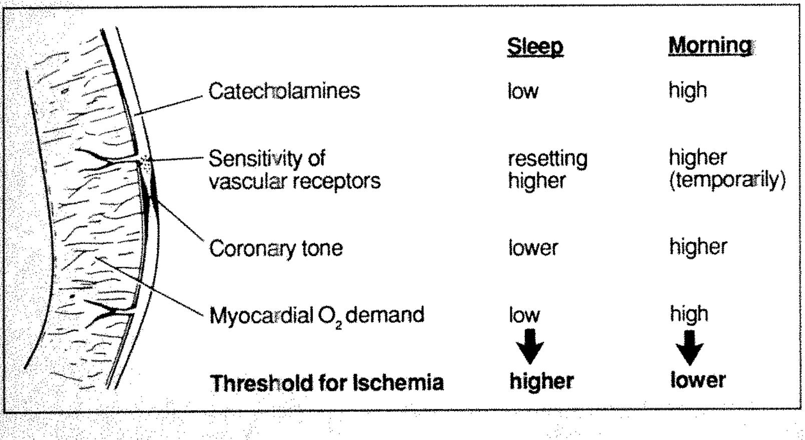
Angiographic studies that have examined the response of large epicardial coronary arteries to similar provocations support a potential relation between coronary artery reactivity and reversible myocardial ischemia. Mental arithmetic tasks such as serial 7 subtraction, forearm immersion in ice water and supine exercise have all been shown to result in a paradoxical constriction of irregular or stenotic coronary artery segments while vessel diameter is seen to increase in normal coronary arteries when similar tasks are performed.[19-21] It is interesting that in the same patients, the unexpected coronary vasoconstriction associated with exercise parallels the response to intracoronary acetylcholine infusion.[21]

PHYSIOLOGIC EVENTS DEMONSTRATING DIURNAL VARIATIONS

Many physiologic processes that are influenced by the time of day or the sleep/wake cycle may at least partially explain the timing of transient ischemia (Fig. 3). Plasma and urinary catecholamines have been shown to increase in the morning hours soon after waking.[22] This may cause the reported morning increases in systolic blood pressure, heart rate, noninvasive measures of cardiac output and left ventricular wall stress.[23-25] These events, potentially enhanced by an abrupt increase in physical activity on waking, may result in increased myocardial oxygen demand in the morning hours. Quyyumi and co-workers[26] have suggested that coronary vascular resistance may follow diurnal patterns. By demonstrating that the heart rate threshold at the development of ST-segment depression during graded exercise was lowest in the morning and late evening and that this occurred at times when postischemic forearm vascular resistance was greatest, the investigators were able to conclude that the temporal pattern of ischemic threshold was potentially due to diurnal changes in coronary vascular resistance mimicking those seen for peripheral vascular resistance. In addition, our studies have demonstrated that patients with coronary artery disease undergoing ambulatory monitoring are more likely to develop ST-segment depression when their heart rates are within the threshold range for developing ischemia during the morning hours compared to the later afternoon and evening.[10] Both of these observations suggest that variations in coronary artery resistance and flow over 24-hour periods may result in different thresholds for developing ischemia at different times of the day. Yasue et al,[27] performing early-morning and late-afternoon angiographic studies, have reported a greater percent increase in coronary artery diameter after nitroglycerin administration in the morning compared to the afternoon. This was interpreted as a sign of a greater degree of coronary vascular tone in the morning compared to other times of the day.

RESPONSE TO THERAPY

Many studies have now demonstrated that β blockers can be used to eliminate the morning increase of transient ischemia, heart rate and blood pressure measured during ambulatory electrocardiographic monitoring.[4-6] This effect of β blockers suggests a potential mechanistic relation between increased myocardial oxygen demand and diurnal variations of ischemic events. Some studies[5] have



	Sleep	Morning
Catecholamines	low	high
Sensitivity of vascular receptors	resetting higher	higher (temporarily)
Coronary tone	lower	higher
Myocardial O_2 demand	low ↓	high ↓
Threshold for Ischemia	**higher**	**lower**

FIGURE 3. Hypothetical mechanisms for an altered threshold for ischemia in the early morning hours. Morning increases in myocardial oxygen (O_2) demand possibly related to increases in catecholamines or extrinsic activity and enhanced coronary artery tone related to a differential response to vasoconstrictive stimuli or altered sensitivity of vascular receptors likely interact to result in a lower threshold for ischemia in the morning hours.

suggested that calcium antagonists alone are not as effective as β blockers in eliminating this diurnal pattern. However, other preliminary studies[6] suggest that the addition of α blockade to less potent β blockade may be as effective at eliminating morning ischemia as the more potent β blockade alone. The effect of coronary vasodilators on diurnal patterns of myocardial ischemia needs further investigation.

In addition, Gaglione et al[28] have demonstrated that, in patients with coronary artery disease receiving pretreatment with intracoronary propranolol before supine bicycle exercise, the vasoconstrictive response to exercise at the site of arterial stenosis can be effectively eliminated. This effect appeared to be limited to the diseased vessel, since propranolol did not influence the response of normal coronary arteries to exercise. This suggests that the efficacy of β blockers in the treatment of coronary artery disease may not be due solely to a reduction in myocardial oxygen demand, but also to vasodilation of stenotic coronary arteries. Whether the same response would be seen with oral β blockers and whether β-blocker-induced vasodilation may play a role in the elimination of morning increases of transient ischemia is not clear at this time.

Nevertheless, these preliminary therapeutic trials suggest that the mechanisms contributing to a morning increase in ischemic activity are likely multifactorial and treatment strategies may need to use combined therapy. The information to date suggests that β blockers may have a role in reducing morning ischemic events and that longer acting or slow-release drug preparations may offer more systematic and stable pharmacologic protection during the increased risk period soon after waking.

CONCLUSION

Transient myocardial ischemia is a frequent event in patients with coronary artery disease and is most common in the morning hours after waking. Various activities have been shown to adversely affect the supply/demand ratio in patients with atheromatous disease by increasing determinants of myocardial oxygen consumption or decreasing coronary supply, or both. The response to various stimuli may be different throughout a 24-hour time period due to diurnal variability in factors contributing to myocardial work or differences in the coronary artery response to vasoactive stimuli. The parallels between the timing of transient ischemia and infarction and sudden death are of interest. It is not likely, however, that platelet aggregability or thrombosis play an important role in the occurrence or timing of stable reversible ischemia, although these factors appear to be important in the genesis of catastrophic cardiovascular events. The pathophysiologic mechanism responsible for transient ischemia in the patient with a stable coronary plaque is complex and may be quite different from that responsible for infarction in the patient with an unstable or ruptured plaque. Nevertheless, a better understanding of how and when certain activities trigger transient increases in myocardial work and coronary vasoconstriction may lead to improved methods of treatment and prevention.

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Application of Time Series Analysis to Circadian Rhythms: Effect of Beta-Adrenergic Blockade Upon Heart Rate and Transient Myocardial Ischemia

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Circadian variations of transient myocardial ischemia and heart rate have been identified, but the rhythms and their response to β blockade have not been fully characterized. Time-series analysis, a mathematical technique to describe oscillatory activity occurring within a continuous data set was used, to address these issues. Nine men with coronary artery disease underwent 72 hours of ambulatory electrocardiographic monitoring during therapy with placebo or metoprolol. During administration of placebo, ischemic time and heart rate showed a primary peak with a periodicity of approximately 24 hours with a tight coupling between the 2 variables and a secondary peak with a periodicity of 5 to 8 hours. During metoprolol therapy, heart rate and ischemic variation were reduced and the 24-hour periodicity for heart rate only remained. The 24-hour periodicity for ischemia was eliminated, but the data with 5- to 8-hour periodicity became the major component of the signal.

(Am J Cardiol 1990;66:22G–24G)

Ischemic vascular events, be they coronary or cerebral, exhibit circadian rhythmicity with an increase of occurrence that begins after waking and persists for several hours. That these events predominate during this time period suggests that the "physiologic milieu" may be optimal for the generation of ischemia. Adrenergic activity, assessed from analysis of time-related alterations in hemodynamic parameters[1] and catecholamine levels,[2] peaks during this same morning time period. This apparent direct relation suggests the hypothesis that they are closely linked not only in time but also in mechanism.

Regression analysis using sin or cosinor harmonic models has been applied to such periodic data by ourselves and others. These methods, however, provide only limited descriptive information. For this reason we used frequency and correlation-based techniques of time series analysis, which have provided useful information in the investigation of other time-varying or pulsatile physiologic signals. Not only do these techniques permit identification of the presence of regular oscillatory activity occurring within a continuous data set, but they also allow objective evaluation of potential intervariable relations. Accordingly, the goals of this study were several: (1) to confirm the presence of circadian rhythms of transient myocardial ischemia and heart rate; (2) to better define their frequency characteristics; (3) to examine their coupling in time; and (4) to examine the influence of the β_1-adrenergic nervous system on these "pulsatile" functions. To accomplish this we used 72-hour, high fidelity recording of ST-segment deviation, and time series analysis.

METHODS

A detailed description of the methods, techniques and results of time series analysis used here has been published in detail elsewhere.[3] Briefly, 9 men with angiographically proven severe (>70% diameter reduction in at least 1 major epicardial coronary artery) coronary artery disease (CAD), a painless positive exercise test electrocardiographic response and either absent or minimal infrequent symptoms were studied. All underwent positional tests, Valsalva and hyperventilation maneuvers, and none exhibited ST-T wave lability with these maneuvers. None were taking medications with an effect on the heart, and all had exhibited at least 10 minutes of asymptomatic transient myocardial ischemia on prior ambulatory electrocardiographic monitoring (AEM).

The study design consisted of 1-week treatment periods (either placebo or metoprolol) with AEM carried out

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for the last 72 hours of each period using Oxford FM 3500 series tape records. The details of metoprolol dosing are described elsewhere.[4] Ischemic episodes were defined as ≥1 mm horizontal or downsloping ST segments, 80 ms after the J point, lasting at least 60 seconds and not associated with symptoms as recorded in a daily diary.

TIME SERIES ANALYSIS

Time series analysis uses complex mathematical techniques to describe oscillatory activity occurring within a continuous data set. These methods have recently been applied to biologic systems, specifically the pulsatile secretion of hormones.[5] Fourier transformations analyze frequency components of time-related data to determine their relative contribution (in terms of spectral power) to the data set as a whole. Autocorrelation analysis, by generating an exact copy of the data and shifting it in time (lag) was used to define the presence of a periodic function. By definition, the autocorrelation function will approach 1 at a lag that is equal to the period of the function (i.e., 24 hours for a circadian rhythm). Finally, cross correlation was used to compare periodic variables. By definition, if they are identical, the cross-correlation function will approach 1 at a lag (time delay) of 0.

RESULTS

Raw data for heart rate and total ischemic time were plotted as a continuum over the 72-hour monitoring period. The time series analyses before and after β blockade are illustrated in Figures 1 and 2. During the placebo phase, circadian variation in heart rate was observed with a periodicity of approximately 24 hours ($p < 0.05$). A similar pattern, though not reaching statistical significance, was noted for total ischemic time. Tight coupling between the circadian rhythms of these 2 parameters was demonstrated by a highly significant cross-correlation function at a lag of 0. The major component (relative spectral power) of both the heart rate and ischemia signals was concentrated at a peak of about 24 hours. Of note was the secondary peak in oscillatory activity found in the 5- to 8-hour frequency range for total ischemic time.

During β_1 blockade (Fig. 2), heart rate maximal and minimal values were markedly attenuated although the spectral content was similar to the placebo period. Thus, although the variation was reduced, the periodicity was concentrated around 24 hours. Total ischemic time variation was similarly altered during β_1 blockade. The spectral characteristics, however, now suggested that the major component of the signal was made by persistence of only the lower frequency (5- to 8-hour) oscillations, as the prominent component that centered about 24 hours was now absent.

DISCUSSION

Little doubt exists among investigators that prominent circadian rhythms occur for many of the manifestations of acute ischemic syndromes. The focus of current

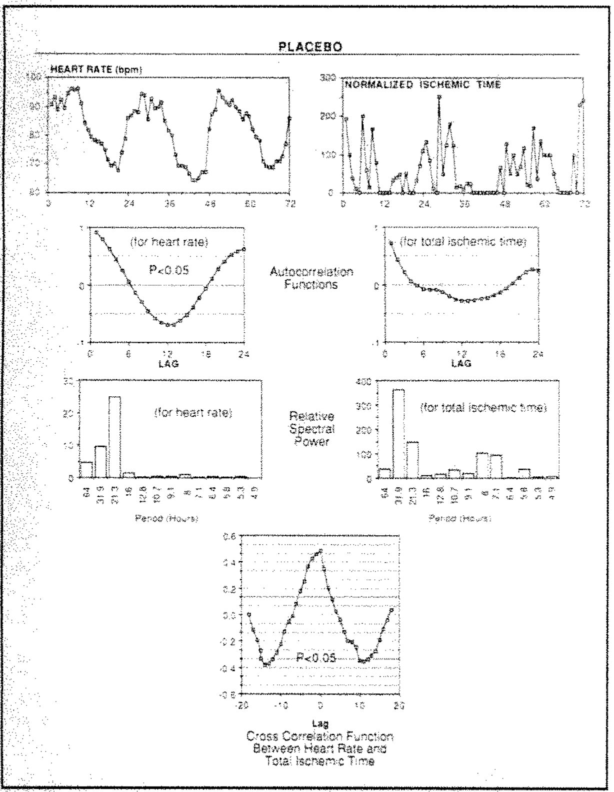

FIGURE 1. Raw data for mean heart rate, total ischemic time and their respective time series analysis during placebo. (Adapted from *Am J Cardiol.*[3])

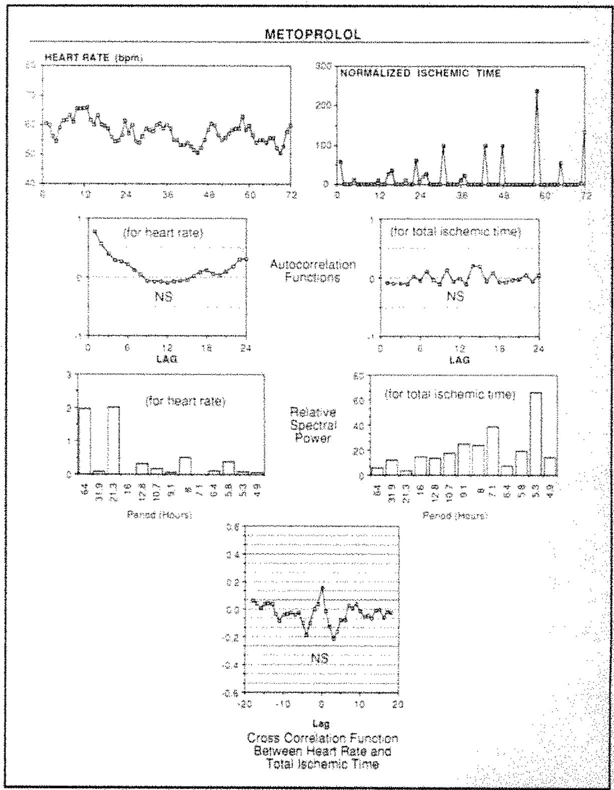

FIGURE 2. Results of the treatment phase with optimal dose metoprolol. NS = not significant. (Adapted from *Am J Cardiol.*[3])

studies has turned toward attempts at identifying the underlying pathophysiologic mechanisms. Our group has focused on the common circadian rhythms noted for daily episodes of transient asymptomatic myocardial ischemia and heart rate recorded during ordinary ambulatory living. Previous work suggests that heart rates are consistently lower just before and during transient ischemia detected during ordinary daily activity, compared with ischemia evoked in the same patient during treadmill exercise testing.[6,7] More definitive conclusions about heart rate and heart rate changes in relation to onset of ischemia cannot be determined during AEM because ST-segment changes are a rather late manifestation of ischemia. Furthermore, their onset is characterized by a continuous rather than an abrupt change. Thus, attempts to relate heart rate changes and ischemia more precisely may be inaccurate and even misleading. For these reasons the method of time series analysis was used. Our results clearly demonstrate coupled circadian rhythms for heart rate and ischemia with a periodicity of approximately 24 hours. Treatment with a β_1 blocker, which exerts a well-known beneficial therapeutic response predominantly by lowering myocardial oxygen demand or parameters such as heart rate, markedly alters the circadian rhythms of both simultaneously recorded heart rate and ischemia. Furthermore, the temporal coupling observed between the same 2 circadian rhythms was abolished.

Clearly, no direct cause-and-effect relation can be established from these data; however, they do imply the importance of demand-site parameters in the generation of daily ischemia detected by AEM.

The observation that the ischemic episodes that centered about a period of 24 hours were either eliminated or markedly reduced with relative sparing of episodes in the 5- to 8-hour frequency range is interesting. One possible explanation may be that heterogeneity exists in the pathogenetic mechanisms responsible for these episodes of daily ischemia. The episodes with periodicity of 24 hours may be more dependent on myocardial oxygen demand (thus, their sensitivity to β_1-adrenergic receptor blockade). Conversely those episodes in the 5- to 8-hour frequency band may be more dependent on supply-side parameters, and this observation could explain their relative lack of response to β_1 blockade.

One may further surmise considerable overlap in this broad categorization, with still other episodes having contributions of supply and demand in varying levels. Effects of β blockers other than decrease of myocardial oxygen demand may be of importance. Preliminary data suggest that they may have antiplatelet effects as well as effects on collateral flow, which further complicate the issue.[8,9] Other potential explanations for our findings include the variability in sympathetic-parasympathetic balance,[10] or the fluctuations in coronary tone that lead to alterations in ischemic thresholds.[11]

CONCLUSIONS

The use of prolonged monitoring periods in patients with severe CAD has allowed the application of the methods of time series analysis as originally described by Box and Jenkins.[12] In addition to confirming circadian rhythmicity of transient ischemia and heart rate and characterizing their periodicity, these methods have provided insight into the effects of pharmacologic intervention. The uncoupling of transient ischemia and heart rate with β_1 blockade should provide the impetus for further therapeutic trials, not only with single agents but also with combination therapy. The ultimate goal of forecasting and controlling periodic cardiovascular ischemic events should be facilitated by further application of time series analysis.[12]

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Transient Myocardial Ischemia and Its Relation to Determinants of Myocardial Oxygen Demand

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Because of conflicting data and a clear need to establish the relative role of increase in myocardial oxygen demand versus reduction in coronary blood flow in the causation of transient ischemia, the role of heart rate and blood pressure changes immediately preceding and during the transient ischemic events observed during daily life were evaluated in 25 patients with coronary artery disease. Elevations in heart rate before onset of ischemia were observed in 61% of the episodes. Similarly, 73% of the ischemic events were preceded by an increase in arterial pressure. These data provide evidence for a significant role of increased myocardial oxygen demand in the genesis of transient myocardial ischemia.

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Simultaneous ambulatory electrocardiographic and blood pressure monitorings were performed in 25 male patients with proven coronary artery disease and established history of chronic stable angina.[1] Patients were instructed to perform their regular activities and maintain a precise record of angina attacks and nitroglycerin consumption during the monitoring sessions. Transient ischemic events were defined using the 1 × 1 × 1 rule, which requires at least 1-mm ST-segment depression that lasts at least 1 minute and is separated from the other events by at least a 1-minute interval. During a total monitoring period of 650 hours, 92 transient ischemic events meeting these diagnostic criteria were observed. Of these, 92% of the events were asymptomatic. Separate baseline heart rate and blood pressure values were calculated during hours of sleep and awake periods by averaging all available values during a 2-hour recording period free of transient ischemic activity. These baseline heart rate values were then compared with the corresponding heart rate values at 1 minute preceding, at 1-mm ST-segment depression and at peak ST-segment depression during the transient ischemic event (Table I).[4] Similarly, the baseline systolic blood pressure values were compared to the corresponding values obtained within 10 minutes preceding, at 1-mm ST-segment depression and at peak ST-segment shifts. Sixty-one percent of the transient ischemic events were preceded by a significant increase in the heart rate. The systolic blood pressure measured within an average of 6 minutes preceding the transient ischemic events also showed a significant increase in 73% of the events with the available blood pressure data.[1] As expected, both heart rate and systolic blood pressure values increased further at 1-mm and peak ST-segment depressions. These data demonstrate that increases in heart rate and systolic blood pressure clearly precede the onset of transient ST-segment depression. Since both heart rate and blood pressure are major determinants of myocardial oxygen demand, our data provide evidence for the role of increased myocardial oxygen demand in the genesis of transient myocardial ischemia during daily life.[1]

Our results[1] are similar to those reported by Quyyumi and coworkers,[2] who demonstrated that over 97% of transient ischemic events were preceded by an increase in the heart rate. Similar findings have also been reported by Hausmann et al,[3] who showed that the heart rate increased >10 beats/min preceding the ST-segment depression in 95% of silent ischemic episodes.

Indeed, some episodes of transient myocardial ischemia are not preceded by a significant increase in heart rate or blood pressure. These events must occur as a result of transient reductions in coronary blood flow caused

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TABLE I Changes in Heart Rate and Systolic Blood Pressure Values Before Onset of ST-Segment Depression, at 1 mm and at Peak ST Depression Observed During Silent Ischemic Events Recorded During 24-Hour Ambulatory Monitoring

	Baseline		Transient Ischemic Events		
	Daytime (awake)	Nocturnal (sleep)	Before Event	1-mm ST↓	Peak ST↓
Heart rate	73 ± 13	59 ± 8	75 ± 17*	92 ± 19*	100 ± 20*
Systolic BP	121 ± 15	111 ± 15	130 ± 18*	138 ± 22*	142 ± 22*

* p <0.001 compared with corresponding baseline.
The values shown are mean ± standard deviation.
BP = blood pressure; ↑ = increasing; ↓ = decreasing.

TABLE II Comparison Between the Heart Rate and Systolic Blood Pressure Values at Baseline, Before Onset of ST Depression, at 1 mm and at Peak ST-Segment Depression During Nocturnal Versus Daytime Transient Events

		Transient Ischemic Events		
	Baseline	Before Event	1-mm ST↓	Peak ST↓
Heart rate				
Daytime, (awake)	71 ± 14	76 ± 17*	94 ± 20†	101 ± 21†
Nocturnal, (sleep)	62 ± 8	71 ± 12*	80 ± 9†	92 ± 12†
Systolic BP				
Daytime, (awake)	122 ± 18	130 ± 18*	137 ± 26†	143 ± 21†
Nocturnal, (sleep)	107 ± 21	118 ± 22‡	137 ± 22*	140 ± 25†

* p <0.05; † p <0.001 compared with respective baseline; ‡ difference not significant.
The values shown are mean ± standard deviation.
Abbreviations as in Table I.

primarily by coronary vasospasm or platelet aggregates that may release vasoconstrictor substances. Thus, it would be reasonable to conclude that, depending on the patient population studied and the activity level preceding the transient ischemia, an increase in myocardial oxygen demand or a transient reduction in coronary blood supply plays a significant role in the genesis of transient myocardial ischemia. Although in some patients one or the other mechanism may play a predominant role, it is logical to think that in most patients a combination of increased oxygen demand and reduced coronary blood flow is involved in the pathogenesis of transient ischemic activity.

NOCTURNAL VERSUS DAYTIME TRANSIENT MYOCARDIAL ISCHEMIA

Since the transient myocardial ischemia during the awake period usually occurs with some kind of physical activity, the pathogenetic role of increased myocardial oxygen demand is well accepted. However, since nocturnal ischemia occurs while the patient is asleep, it is generally believed that reductions in coronary blood flow due to coronary artery spasm play a dominant role in the genesis of ischemia during hours of sleep. In a recent study, Quyyumi et al[2] have shown that, in patients with atherosclerotic coronary artery disease, a vast majority of nocturnal resting ischemic episodes are preceded by an increase in heart rate (Fig. 1). Although these findings do not necessarily establish the role of increased oxygen demand in the genesis of transient ischemic episodes during sleep, they do provide suggestive evidence.

Since more definitive evidence could be established by evaluation of simultaneous changes in heart rate and blood pressure, we evaluated the role of such changes during simultaneous 24-hour electrocardiographic and

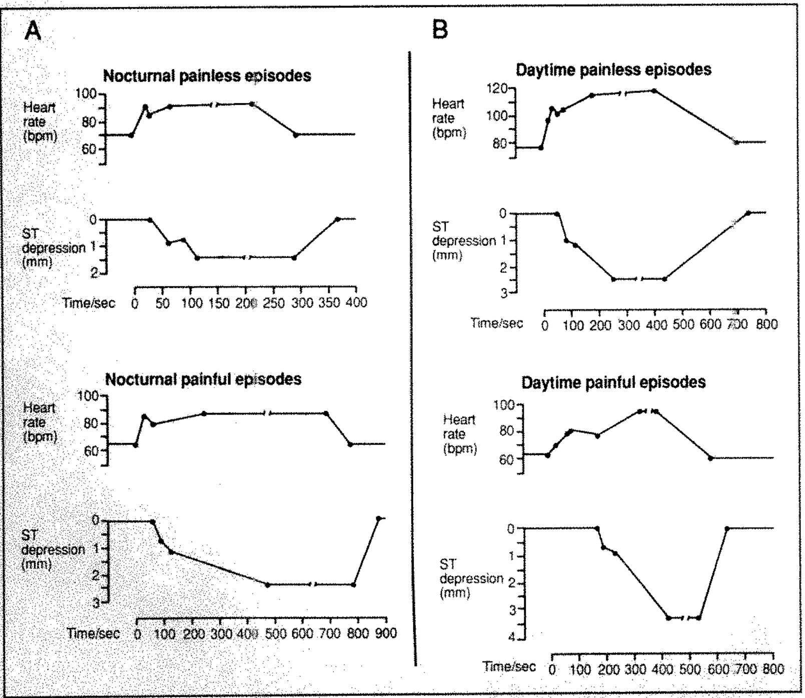

FIGURE 1. Comparison between mean heart rate changes preceding and during painless and painful nocturnal ischemic episodes in 5 patients (*A*), versus the same changes during daytime painless and painful episodes in 11 patients (*B*). (Adapted from *Lancet*.[2])

blood pressure monitoring performed in patients with proven coronary artery disease and stable angina. In these patients, using the techniques and evaluations described in the previous section, we compared the changes in heart rate and systolic blood pressure preceding the transient ischemic episodes observed during awake and sleep hours in the same patient. As listed in Table II, comparison of these changes between daytime and nocturnal transient ischemic events shows a significant ($p < 0.05$) increase in heart rate preceding the events. The systolic blood pressure values also show an increase, but because the blood pressure values are not available for a large number of nocturnal episodes, these changes do not achieve statistical significance.

The exact mechanism responsible for the increase in heart rate and blood pressure preceding the nocturnal transient ischemic events is not known. The results of polysomnographic monitoring suggest that disturbed sleep and dreams, as well as changes in posture, may play a role.

CIRCADIAN RHYTHMICITY OF TRANSIENT MYOCARDIAL ISCHEMIA AND THE ROLE OF INCREASED OXYGEN DEMAND

Based on the results of available studies, there remains little doubt that transient myocardial ischemia occurs with similar circadian rhythmicity as does acute myocardial infarction and sudden cardiac death. Several studies[5,6] have shown that transient ischemic attacks show the highest density during the morning hours, reaching a plateau around noon, with another peak in the late evening hours. Although the precise mechanism responsible for the circadian rhythmicity of transient myocardial ischemia is not known, several possible factors have been postulated. There is a parallel surge in the heart rate and blood pressure during the morning hours, causing an increase in myocardial oxygen demand. Similarly, myocardial contractility also increases secondary to increased epinephrine levels, causing a further increase in oxygen demand. Although these increases in the determinants of oxygen demand clearly point toward a role of increased demand in the pathogenesis of transient myocardial ischemia, several other important possibilities exist and may play a role in the matutinal surge of transient ischemia. Increased platelet aggregability and coronary vasomotor tone have been demonstrated during the morning hours and may result in reduced coronary blood flow. Although the precise role of each of these changes has not been established, it is likely that a combination of these factors may be responsible for the circadian rhythmicity of transient myocardial ischemia. Indirect evidence available from some recent studies showing significant reduction in the morning surge of ischemia with β blockers suggests that increases in heart rate and blood pressure secondary to the increased catecholamine levels must play a significant role.

CLINICAL IMPLICATIONS

This review of the role of increased myocardial oxygen demand in the pathogenesis of transient myocardial ischemia has significant clinical implications. If increase in myocardial oxygen demand, as shown by increased heart rate and blood pressure response preceding the transient ischemic events, plays a significant role, the ideal therapeutic agent would be a β-blocking agent. The administration of a long-acting β blocker providing 24-hour protection could also prevent the morning surge in ischemic activity and may cause reduction in the associated catastrophic events of myocardial infarction and sudden cardiac death. Although definitive studies are lacking, preliminary findings of some recent studies indeed demonstrate the efficacy of β blockers in reducing the number, duration and the morning surge of transient myocardial ischemia.[6,7]

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Mental Stress as an Acute Trigger of Ischemic Left Ventricular Dysfunction and Blood Pressure Elevation in Coronary Artery Disease

C. Noel Bairey, MD, David S. Krantz, PhD, and Alan Rozanski, MD

Acute mental stress may be a frequent trigger of transient myocardial ischemia, myocardial infarction and sudden cardiac death. In an experimental setting, the effect of mental stress on hemodynamics and left ventricular wall motion abnormalities (as detected by radionuclide ventriculography) was measured in 29 patients with exercise-induced myocardial ischemia. Seventy-five percent of the patients demonstrated mental stress-induced wall motion abnormalities. Patients frequently exhibited greater increases in peak systolic arterial pressure during mental stress than during exercise.

Personally relevant mental stress is the most potent type of mental stress, both in terms of frequency and magnitude of ischemia. Most mental stress-induced ischemic episodes are clinically and electrocardiographically silent and occur at heart rates significantly lower than those seen during exercise. Both systolic and diastolic blood pressure increased during mental stress-induced ischemia, suggesting that increased myocardial oxygen demand plays a role in the pathophysiology of mental stress-induced transient ischemia. The significant magnitude and acute onset of this mental stress-induced blood pressure elevation may in some manner contribute to atherosclerotic plaque rupture. These findings may provide a pathophysiologic link to the epidemiologic association between mental stress and acute ischemic coronary events. A new ambulatory radionuclide detector that can concurrently monitor left ventricular ejection fraction and electrocardiographic ST-segment change may enhance the detection and evaluation of transient myocardial ischemia in ambulatory coronary patients.

(Am J Cardiol 1990;66:28G–31G)

There is a common perception within the lay and medical communities that mental stress can be a precipitant of acute myocardial ischemia and coronary events. For instance, anecdotal reports such as the following abound: "A physician, 53 years old, who had suffered a myocardial infarction a couple of years earlier, reacted with outrage when told by his chief that he was not to be the choice to succeed him. He soon composed himself, but 4 days later, a few hours after a chance meeting with the chief, he again became angry in the presence of witnesses; he collapsed and died but not before an electrocardiogram had shown ventricular fibrillation."[1]

Although some epidemiologic studies support the notion of an association between heightened mental stress and ischemic cardiac events,[2,3] these inquiries have not been definitive nor have they helped to identify the pathophysiology by which this occurs.

Recently, new technologies have given investigators the opportunity to study the relation between mental stress and ischemic cardiac events more closely. Studies using ambulatory ST-segment monitoring suggest that mental stress may play an important role in transient myocardial ischemia: Barry et al[4] have observed a propensity toward more frequent ischemia when mental stress is intensified during daily activity; and Freeman et al[5] report similar findings.

Multiple studies of transient ischemia during ambulatory monitoring have disclosed that most ischemic episodes are silent; they occur at relatively low heart rate elevations, compared to exercise heart rates; they exhibit a characteristic circadian rhythm; and they vary greatly in frequency over time.[6] These characteristics parallel aspects of mental stress encountered in everyday life and suggest that such stress may trigger transient myocardial ischemia.

STUDY DESIGN

Using a controlled experimental setting, we designed a protocol to assess the role of mental stress as a precipitant of ischemic left ventricular (LV) dysfunction in patients with coronary artery disease (CAD).[7] Using radionuclide ventriculography as a sensitive indicator of ischemia, we evaluated 39 patients with CAD for exercise-induced ischemia, as evidenced by electrocardiographic or radionuclide imaging techniques, or both. We found that 29 patients had exercise-induced ischemia and 10 did not. A control group of 12 subjects had no clinical or exercise test evidence of CAD.

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After initial baseline parameters were determined, both groups underwent maximal bicycle exercise testing, preceded by 4 sequential mental tasks: (1) math test—serial subtractions of the number 7 from a 4-digit number, with periodic criticism and a metronome ticking loudly in the background; (2) Stroop color-word test—a rapid slide presentation of different names displayed in different colors of ink, with instructions to report the color and not the written name. Patients were frequently told they were incorrect or that they were not responding quickly enough; (3) speech test—giving a 5-minute impromptu speech regarding one's personal faults or undesirable habits, in front of 2 observers; and (4) reading test—reading out loud from a paper on a neutral topic. This was a control task for the physical act of speaking.

Radionuclide ventriculograms, heart rates, blood pressure measurements and 12-lead electrocardiograms were obtained during testing. The radionuclide ejection fractions were calculated by an experienced operator.[8] LV wall motion was scored by 2 experienced observers who were blinded to the clinical data and the order of images used for testing.

RESULTS

Overall response to mental stress testing is shown in Figure 1. Twenty-one (75%) of the 29 patients with CAD and exercise-induced ischemia had corresponding mental stress-induced ischemia, as evidenced by wall motion abnormalities. This percentage contrasted strikingly with both normal control subjects and those patients with CAD but without obvious evidence of exercise-induced ischemia. The magnitude of wall motion abnormalities induced by the "worst" mental tasks was substantial in that it was comparable to that induced by exercise. (The speech task was designed to be the most "personally relevant," and it was the most potent in terms of frequency and magnitude of all ischemic indicators.)

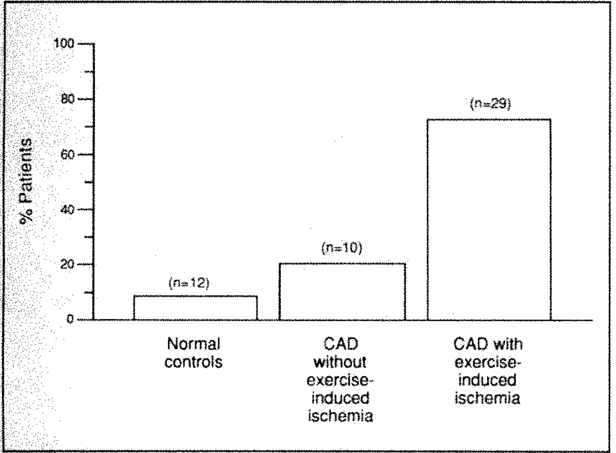

FIGURE 1. Wall motion abnormalities during mental stress testing. Percentage of patients experiencing mental stress-induced wall motion abnormalities. Twenty-one (75%) of the 29 patients with exercise-induced ischemia had wall motion abnormalities during mental stress, in striking contrast to the patients with coronary artery disease (CAD) without exercise-induced ischemia and normal control subjects.

Of the 39 patients with CAD, with or without wall motion abnormalities, 14 (36%) had LV ejection fractions that decreased significantly (>5%) during mental stress. Ejection fractions did not decrease in the control group. These results demonstrate that mental stress can be a potent trigger for significant ischemic LV dysfunction in patients with CAD.

MENTAL STRESS-INDUCED ISCHEMIA

Of the 21 patients with wall motion worsening during both mental stress and exercise, only 4 (19%) had chest pain during mental stress-induced ischemia, compared with 10 (48%) during exercise. We found that electrocardiography was an insensitive detector of ischemia compared to radionuclide ventriculography. Among the 21 patients with mental stress-induced wall motion worsening, only 6 (29%) had significant concurrent ST-segment depression. These results mirror exercise test results in which radionuclide indexes were found to be more sensitive than electrocardiography for detecting ischemia.[9]

Our laboratory protocol provided the unique opportunity to further assess some of the "demand" aspects of transient ischemia induction. Peak heart rates obtained

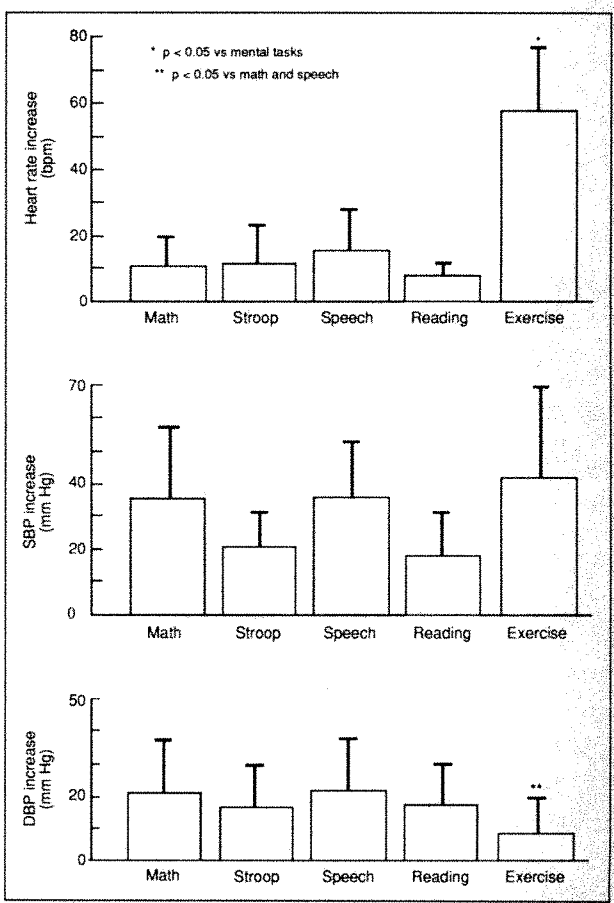

FIGURE 2. Hemodynamic responses (mean ± standard deviation) to mental tasks, as compared to exercise testing. Note that systolic blood pressure (SBP) was often dramatically elevated during mental tasks and that diastolic blood pressure (DBP) measurements were higher for mental tasks than for exercise. (Adapted from *N Engl J Med.*[7])

TABLE I Mental Stress-Induced LV Dysfunction Assessed by Differing Modalities

Investigators	Modality	Measure(s) Assessed
Rozanski et al[7]	Radionuclide ventriculography	LV wall motion, LVEF
Breisblatt et al[10]	Ambulatory radionuclide monitor (VEST)	LVEF
La Veau et al[11]	Nuclear probe (nuclear stethoscope)	LVEF
Gottdiener et al[12]	Echocardiography	LVEF, LV wall motion

EF = ejection fraction; LV = left ventricular.

during the performance of mental tasks, while significantly elevated from baseline conditions, were much lower than heart rates obtained during exercise (Fig. 2). This result, along with the "silent" nature of mental stress-induced ischemia, parallels the characteristics of transient ischemia that were noted during ambulatory ST-segment monitoring.

Evaluation of acute blood pressure changes, not generally possible during ambulatory electrocardiography, revealed significant elevations in systolic blood pressure during mental stress, often comparable to those elicited during exercise. Sixteen of 39 (41%) of the CAD patients achieved peak systolic blood pressure values during mental stress that were higher than those achieved during maximal exercise. Further, diastolic blood pressure elevations were consistently greater during mental stress testing than during exercise. An example of mental stress-induced blood pressure elevation is shown and contrasted to blood pressure changes during exercise in Figure 3. Thus, although heart rates were relatively low during mental stress testing, another important determinant of myocardial oxygen demand—arterial blood pressure—was significantly elevated.

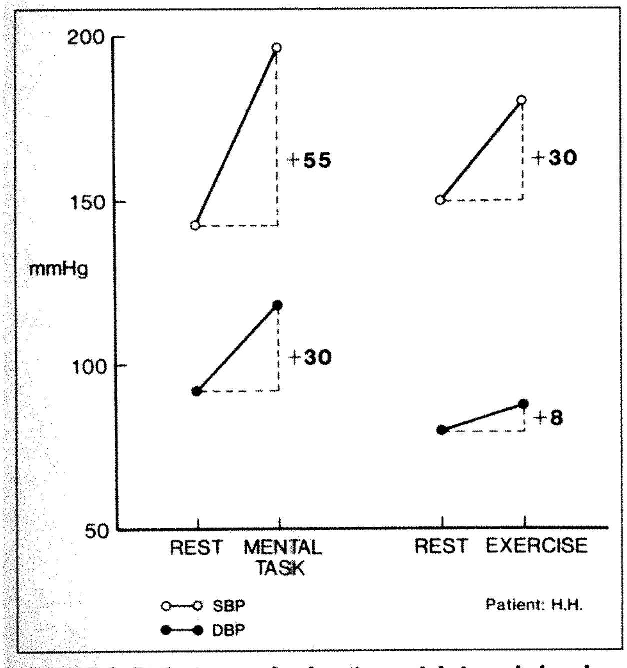

FIGURE 3. Patient example of acute mental stress-induced blood pressure elevation as compared to blood pressure elevation during exercise. During the mental task (speech), peak SBP, DBP and the corresponding net changes were higher during mental stress than during maximal exercise. These hemodynamic changes were accompanied by the development of ventricular septal wall dyskinesis and a significant decrease in left ventricular ejection fraction during mental stress. Abbreviations as in Figure 2.

Since our initial report,[7] other investigators have demonstrated mental stress-induced LV dysfunction using techniques such as ambulatory radionuclide monitoring,[10] a nuclear probe[11] and echocardiography[12] (Table I). Investigators using test protocols and laboratory settings similar to ours report a comparable frequency and magnitude of mental stress-triggered LV dysfunction, thus confirming our findings of the high frequency of mental stress-induced ischemia in coronary patients with exercise-induced ischemia, its "silent" nature and the relative insensitivity of electrocardiography as a laboratory measure of myocardial ischemia during mental stress testing.

Until recently, it was not possible to extend the laboratory investigation of myocardial ischemia by radionuclide techniques to the ambulatory setting. Now, however, an ambulatory radionuclide detector (the VEST, by Capintec, Inc.) has been developed for continuous ambulatory monitoring of LV ejection fractions. The VEST consists of a single sodium iodide detector that measures LV counts every 31 ms during the cardiac cycle. Since counts are proportional to volume, beat-by-beat time-activity (volume) curves can be generated to calculate LV ejection fraction.

We have demonstrated that reproducible measurements of LV ejection fraction can be obtained using the VEST during repetitive physical exercise.[13] We have also recently used this device to evaluate LV ejection fraction response in normal subjects during daily activities.[14] LV ejection fraction response appears to differ among varying stimuli, with predominant increases during physical forms of exercise and modest changes (including decreases) durng mental stress, micturition and hyperventilation in normal subjects. These changes are in part related to heart rate and blood pressure change; however, other factors, such as neurohormonal regulation, may also play a role. In patients with CAD, combined ambulatory monitoring of both the ST segment and LV ejection fraction could enhance our ability to detect and study transient myocardial ischemia.

Acknowledgment: We are grateful to Ann Cummings for her expert manuscript preparation.

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Triggers of Transient Myocardial Ischemia: Circadian Variation and Relation to Plaque Rupture and Coronary Thrombosis in Stable Coronary Artery Disease

Peter H. Stone, MD

The phenomenon of transient myocardial ischemia is common in patients with stable coronary disease and appears to be due both to increases in myocardial demand and to episodic coronary vasoconstriction. The circadian variation of transient ischemic episodes closely parallels the circadian variation of acute coronary syndromes associated with plaque rupture, such as myocardial infarction and sudden death. These concordant temporal patterns of transient ischemia, myocardial infarction and sudden cardiac death probably represent independent manifestations stemming from the consequences of increased sympathetic activity.

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The purpose of this review is to explore the significance of the temporal pattern of occurrence of transient ischemic episodes in patients with stable angina and to explore the relation between episodes of reversible myocardial ischemia and the irreversible disorders of myocardial infarction and sudden death.

TEMPORAL PATTERN OF OCCURRENCE OF AMBULATORY TRANSIENT ISCHEMIA AND IMPLICATIONS CONCERNING PATHOPHYSIOLOGIC MECHANISMS

There has been a remarkable concordance of observations concerning the temporal distribution of ischemia during ambulatory activities, with a peak occurrence as observed by Rocco et al[1] and others[2-6] in the morning hours after awakening. The frequency of ischemic events remains high during the day, becomes less during the evening hours and decreases again during the hours of sleep. This temporal pattern of occurrence very closely parallels the temporal pattern of heart rate and blood pressure observed during a 24-hour period (Fig. 1)[7] and may indicate that increases in heart rate, blood pressure or myocardial contractility—determinants of myocardial oxygen demand—are responsible for the provocation of ischemic episodes.[8] Other physiologic processes display a prominent circadian variation, however, and may also contribute to the provocation of ischemia.[8] Resting coronary tone, for example, is highest in the morning and less intense at night,[9] suggesting that episodic coronary vasoconstriction may also contribute to the process of ischemia. Episodes of increased heart rate in the morning are significantly more likely to result in ischemia than are similar increases that occur in the afternoon or at night.[1] Support for the varying contribution of coronary tone to the ease of provocation of ischemia throughout the day comes from a recent preliminary report by Quyyumi and colleagues[10] that the exercise time to development of 1-mm ST-segment depression among patients with stable angina is significantly shorter in the morning than in the afternoon, and is associated with an increase in systemic vascular resistance in the morning compared to the afternoon. Furthermore, episodes of ischemia during outpatient ambulatory activities have consistently been shown to occur at a lower heart rate than a similar degree of ischemia observed during a supervised exercise test,[1,11-13] suggesting that the threshold of myocardial oxygen demand at which ischemia develops throughout the day

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may vary, presumably due to varying coronary vasomotor tone.

There are many physical and emotional activities that occur during the waking hours that may contribute to the observed circadian variation of transient myocardial ischemia by their effects on both myocardial oxygen supply as well as oxygen demand (Fig. 2). Quantitative angiographic studies have demonstrated that isometric or dynamic exercise, activities characteristically considered to provoke episodes of ischemia by increasing oxygen demand, also may predispose to the development of ischemia by causing significant vasoconstriction in a coronary artery with atherosclerosis.[14,15] Mental stress and cigarette smoking, which are potent stimuli leading to myocardial ischemia,[16-19] are also associated with both increases in myocardial oxygen demand and decreases in oxygen supply. Although systolic blood pressure may increase in response to mental stress and cigarette smoking to the same degree as during exercise, the increase in heart rate in response to mental stress in some studies is significantly less than that observed during exercise testing.[17-19] Specchia and colleagues,[20] however, observed that the double product at the onset of ischemia was the same regardless of whether it was induced by mental arithmetic or physical exercise, suggesting that coronary vasoconstriction need not be implicated in the process of mental stress-induced ischemia. These investigators noted, furthermore, that the subset of patients with stable coronary disease who developed ischemia after mental arithmetic also developed a higher peak double product after mental stress and a shorter exercise duration than those who did not develop ischemia after mental stress, and suggested that these patients exhibited a more generalized heightened sympathetic response to both stimuli. Clearly, both increases in myocardial oxygen demand (increases in heart rate and blood pressure) and decreases in myocardial oxygen supply (episodic vasoconstriction) contribute to the pathogenesis of transient myocardial ischemia during routine ambulatory activities.

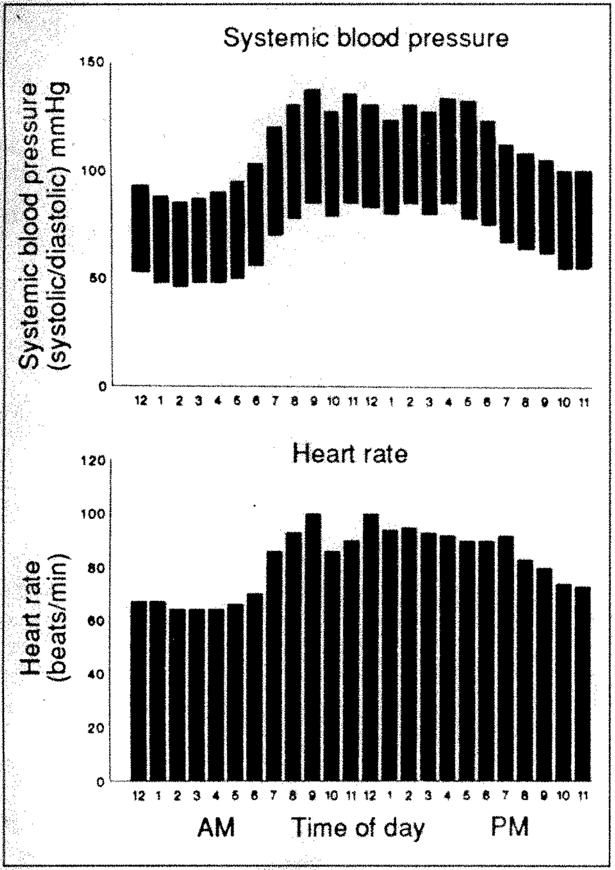

FIGURE 1. Circadian variation in systemic arterial pressure and heart rate. (Adapted from *Circulation.*[8])

The circadian pattern of transient myocardial ischemia also parallels the circadian pattern of platelet aggregability,[21] suggesting that transient platelet aggregates may be related to episodes of ischemia (Fig. 3). However, in patients with stable coronary disease, interventions that reduce platelet aggregability (e.g., ticlopidine) have not been shown to reduce episodes of ambulatory ischemia,[22] and, conversely, interventions that reduce episodes of ambulatory ischemia (e.g., metoprolol) do not alter the morning increase in platelet aggregability (Fig. 3).[4] Although platelets are clearly central to the pathophysiology of unstable angina and acute myocardial infarction, syndromes that are associated with a ruptured atherosclerotic plaque and superimposed thrombus formation,[8] they do not appear to contribute to the manifestations of stable coronary disease.

Further insight into the mechanisms responsible for transient myocardial ischemia can be gleaned from the studies of pharmacologic therapy to treat such episodes. Beta-adrenergic blockers have consistently been found to significantly reduce the frequency and severity of transient silent ischemia,[4,5,23-27] yet β blockers that have intrinsic sympathomimetic activity and, therefore, do not reduce the heart rate, are significantly less effective in treating transient ischemia than are β blockers that do not have intrinsic sympathomimetic activity.[25] Diltiazem, which is also associated with a reduction in heart rate,[26,27] has been found to reduce episodes of transient ischemia,[26-28] although the reduction in heart rate and ischemic episodes is less than that seen with a β blocker.[27] The short-acting formulation of nifedipine, which is associated with a reflex increase in heart rate, has not generally been effective in the treatment of transient ischemic epi-

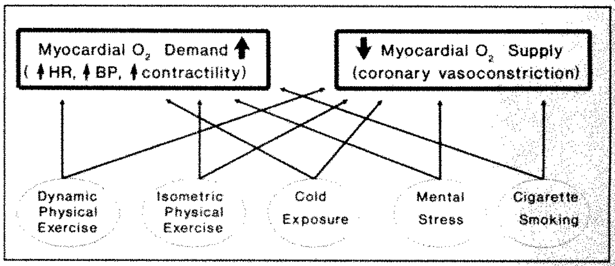
Myocardial O$_2$ Demand ↑
(↑HR, ↑BP, ↑contractility)
↓ Myocardial O$_2$ Supply
(coronary vasoconstriction)
Dynamic Physical Exercise
Isometric Physical Exercise
Cold Exposure
Mental Stress
Cigarette Smoking

FIGURE 2. Effects of routine daily activities on the myocardial oxygen (O_2) supply:demand balance. BP = blood pressure; HR = heart rate; ↑ = increasing; ↓ = decreasing.

sodes when used alone.[27,28] Results from pharmacologic studies suggest that, although episodic vasoconstriction is important in the mechanism of transient ambulatory ischemia, a reduction in heart rate and presumably myocardial oxygen demand, is particularly important to reduce the frequency and severity of ischemia.

RELATION OF TRANSIENT ISCHEMIA TO MYOCARDIAL INFARCTION AND SUDDEN DEATH

There is a remarkable similarity between the circadian pattern of episodes of transient ischemia and that of fatal and nonfatal myocardial infarction, sudden death and stroke (Fig. 4).[8] It remains unclear, however, whether these patterns reflect independent consequences of the same underlying pathophysiologic process, or whether these patterns are causally related (Fig. 5).[8] Beta-adrenergic activity, which increases in the morning after assumption of upright posture[29] and which increases further in response to physical or mental stress, may cause the increase in myocardial oxygen demand that leads to the manifestations of transient ischemia. Episodic vasoconstriction due to the intrinsic diurnal variation of coronary vasomotor tone or to the vasoconstrictive effects of

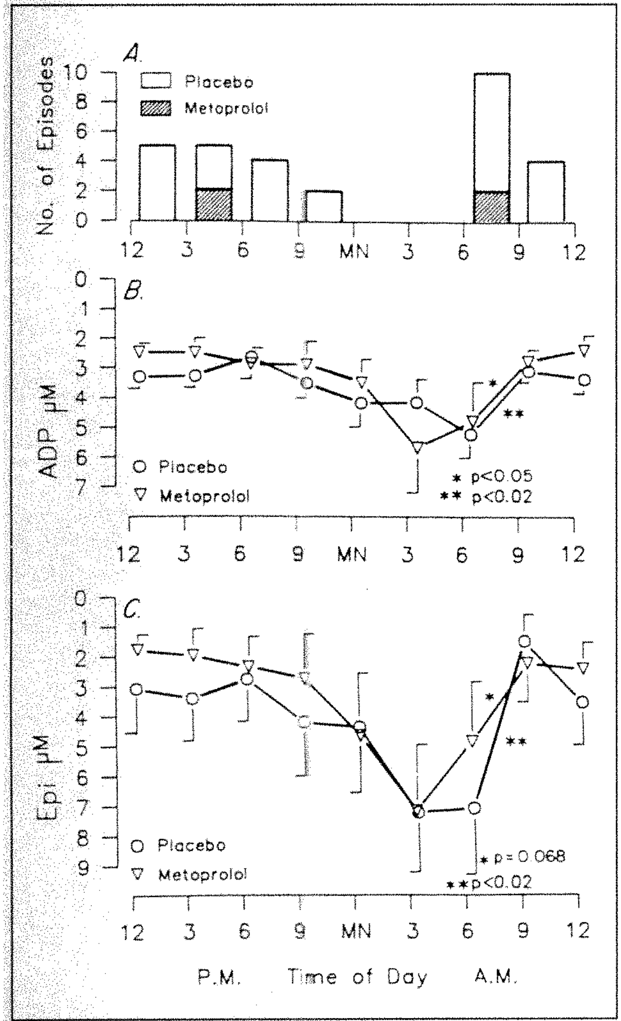

FIGURE 3. Morning increase of silent ischemic episodes (*A*) and threshold concentrations of adenosine diphosphate (ADP) (*B*) and epinephrine (Epi) (*C*) required to produce biphasic platelet aggregation. Compared with placebo, metoprolol reduced the number of silent ischemic episodes (*A*) although it did not significantly alter the morning increase or the midnight (MN) 24-hour level of ADP and epinephrine threshold concentration, indicating that the patients with coronary artery disease have a morning increase in platelet aggregability that is not altered by β blockade. Note that the *y axis* of *B* and *C* have been inverted to indicate that a decrease in threshold concentration reflects an increase in platelet aggregability. (Adapted from *Circulation*.[4])

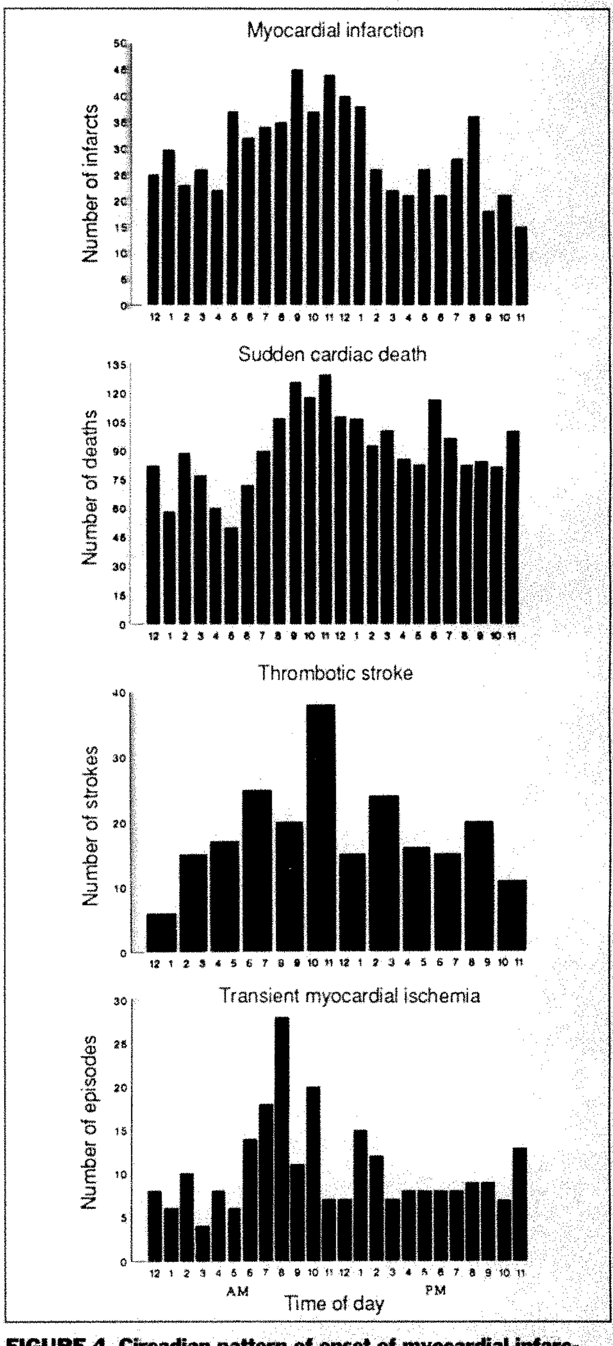

FIGURE 4. Circadian pattern of onset of myocardial infarction, sudden cardiac death, thrombotic stroke and episodes of transient myocardial ischemia. (Adapted from *Circulation*.[8])

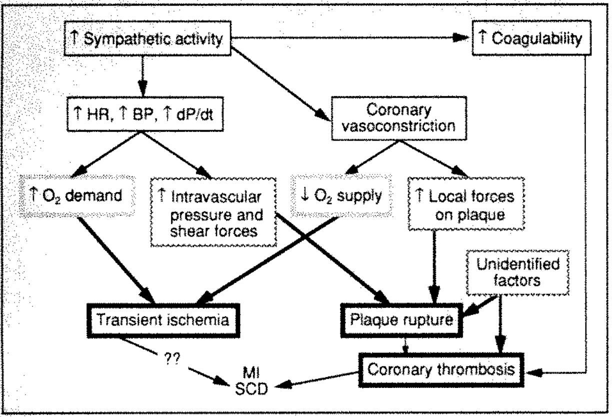

FIGURE 5. Triggering of acute cardiovascular events. Surges of sympathetic activity may lead to episodes of transient ischemia and may also lead to plaque rupture, which in turn leads to coronary thrombosis. See text for discussion. MI = myocardial infarction; SCD = sudden cardiac death; other abbreviations as in Figure 2.

frequent extrinsic activities, such as physical or mental stress or cigarette smoking, may further imbalance the myocardial oxygen supply:demand relation and promote development of transient ischemia.

The same circadian distribution of increased sympathetic activity may exert a very different effect on a vulnerable atherosclerotic plaque (Fig. 5). The increases in heart rate, blood pressure and myocardial contractility may physically stress a plaque, as may the increased local forces exerted on the plaque due to vasoconstriction. These physical stimuli may lead to fissures in the cap of a vulnerable plaque, which then exposes collagen and other plaque contents that form the substrate for thrombus formation. The degree of platelet aggregability and coagulability at the time of plaque rupture may importantly influence whether the plaque fissure leads to occlusive thrombus formation or whether the fissure reseals without leading to a cardiac event.

Surges in sympathetic activity may also increase coagulability, as indicated by studies showing increased platelet deposition on damaged vessel walls after an infusion of physiologic doses of epinephrine in an *in vivo* animal model[30] and by increased platelet aggregability with assumption of upright posture in man.[29] Thus, plaques that rupture in the morning may be more prone to the development of an occlusive superimposed thrombus, whereas plaques that rupture at other times of the day may be more likely to develop a subclinical mural thrombus.

There is no proof at this time that there is a direct or causal relation between episodes of ambulatory ischemia and development of plaque rupture and occlusive coronary thrombosis. Episodes of transient ischemia may lead to sudden death, however, by precipitating arrhythmias. The common association between transient ischemia and myocardial infarction, therefore, appears to be the surges in sympathetic activity that occur throughout the day. Thus, β blockers may be useful to treat or prevent both the reversible and irreversible manifestations of coronary disease, although the mechanism of benefit may be different for the different disease manifestations. For patients with stable coronary disease, β blockers may prevent the increases of myocardial oxygen demand and, to a lesser degree, the coronary vasoconstriction due to increased sympathetic activity, and may thereby prevent episodes of ambulatory ischemia. Beta blockers may also prevent myocardial infarction and sudden death by preventing the physical stresses that trigger rupture of the plaque and stimulate the coagulation system.

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Cause of Thrombosis in Human Atherosclerotic Arteries

Paris Constantinides, MD, PhD

Although it has been known for a long time that thrombosis nearly always develops in atherosclerotic arteries—and almost never in normal vessels—the mechanism through which atherosclerosis promotes thrombosis was unknown until this problem was explored through histologic examination of complete serial section sets of thrombosed atherosclerotic arteries. These studies, repeatedly confirmed, revealed that the thrombi are triggered by microscopic cracks in the collagen cap of advanced plaques. Blood most often seeps from the arterial lumen through the cracks into the underlying lipid gruel before the breaks or cracks are plugged by the thrombi (which function as hemostatic seals of the breaks). These results are parallel to results of experimental studies in which the synergism of endotheliotoxic and pressor agents produced thrombi over cap breaks and sub-break hemorrhages only in arteries with advanced collagen-rich plaques, not in arteries with early atherosclerosis or in normal vessels. This finding indicates that advanced atherosclerosis makes the arterial wall much more fragile and that, once broken, this wall exposes the blood to powerful thrombogenic materials that do not exist in normal arterial tissue. At present, human and experimental evidence suggest that the thrombogenic fissures of advanced plaque caps can be promoted by several factors, such as a surge in intraarterial pressure or insults that damage the caps structurally and increase their vulnerability to any type of stress such as certain metabolic, exogenous chemical and immune insults, spontaneous molecular changes of collagen with time and hemorrhages of capillaries that invade advanced plaques from the adventitia or the arterial lumen.

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When we first became interested in this subject in the late 1950s, it was known that thrombosis almost always develops in atherosclerotic arteries—and almost never in normal vessels—but the mechanism through which this occurs was unknown and therefore subject to much speculation. In the small number of cases in which thrombi developed over ulcerated plaques and the whole cap was blown off and blood clotted over the crater, it was not difficult to understand the process. But in most cases the thrombus developed over a plaque with a seemingly intact fibrous cap and, most frequently, a mysterious hemorrhage in the underlying lipid gruel, as first pointed out by Paterson[1] (Fig. 1). Three main theories attempted to explain the thrombosis over the intact but most frequently hemorrhagic plaques. These were the theory of stasis, the theory of systemic hypercoagulability and the theory that the thrombi result from the hemorrhage of capillaries that invade the plaque directly from the lumen. All 3 were incompatible with known facts. The stasis and hypercoagulability theories could not explain the intraplaque hemorrhages, and, moreover, when extreme systemic hypercoagulability was produced experimentally, it caused thousands of little thrombi in the capillaries and venules of various viscera—not a single thrombus in a single artery over a single plaque. Finally, the luminal capillary hemorrhage theory, which proposed that thrombi are caused by the rupture of thin-walled lumen-derived capillaries because they are directly exposed to the high pressure prevailing within the lumen,[1] could not be reconciled with the fact that most plaques are capillarized from the adventitia rather than from the lumen, among other things.

In the early 1960s we succeeded in producing highly advanced atherosclerosis in rabbits through the intermittent hyperlipemia technique, a procedure that allowed the animals to develop all features of human end-stage plaques, down to their last anatomic detail (including thick collagenic cap, massive calcified lipid gruel with cholesterol crystals and ceroid, destruction of the media and invasion of the plaque interior by the vasa vasorum from the adventitia) within a year or less.[2] We also found that in such animals we could produce thrombi over hemorrhagic plaques by injecting them with a combination of an endotheliotoxic agent (Russell's Viper Venom) and vasoactive agents such as epinephrine, norepinephrine, angiotensin, serotonin or pitressin. Histologic examination suggested that (1) most of these hemorrhages were due to breaks of the plaque surfaces that allowed blood to rush from the lumen into the plaque interior, and (2) the

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thrombi represented hemostatic seals over these surface breaks. A fascinating observation was that these experimental thrombi could be produced only in arteries with advanced fibrous (collagen-rich) atherosclerosis, never in normal vessels or even in arteries with early lesions.[2] We therefore concluded that advanced atherosclerosis changes the arterial wall, making it much more fragile, and that once broken, the atherosclerotic wall exposes the blood to large amounts of powerful thrombogenic materials (such as collagen) that are not present in the normal arterial tissue.

To find out whether thrombosis in human atherosclerotic arteries is triggered by breaks of plaque surfaces, as in our atherosclerotic rabbit experiments, in 1963 we examined complete serial section sets (1 section every 7 μ) from the beginning to the end of the entire thrombosed segment of 20 consecutive coronary artery thrombosis cases coming to autopsy in St Louis,[3,4] and later of 10 consecutive cerebral artery thrombosis cases in Vancouver.[5] After examining more than 50,000 sections we found that in both coronary and cerebral arteries: (1) all thrombi were caused by cracks of plaque surfaces (Fig. 2), and (2) most major hemorrhages in the plaques were clearly due to the entry of blood from the lumen into the plaque interior through these cracks (before the cracks were sealed by the thrombi), even though in a few cases the major lumen-derived hemorrhages were accompanied by smaller capillary-derived hemorrhages at the base of the plaques. It should be emphasized that the majority of the thrombogenic plaque fissures had developed in avascular plaque segments—segments that were not capillarized, and in acellular cap areas—areas in which the cells that produced and maintained the cap collagen had died and disappeared. Since collagen is not immortal but is doomed to disintegrate when the cells that renew it disappear, the latter finding provided a clue to a frequent mechanism of structural cap weakening. Furthermore, in several cases the fissures had developed in very thin caps or at sites of transition between the thick and thin portion of a cap.

Similar findings have since been made in 5 other step-serial section studies of human thrombosed coronary arteries by investigators in the United States, Britain, West Germany and Denmark.[6–10] It thus seems certain now that thrombosis in human atherosclerotic arteries is practically always caused by breaks of plaque surfaces that are usually so small that they can be discovered only with serial sectioning of the entire thrombosed arterial segment (Fig. 3A).

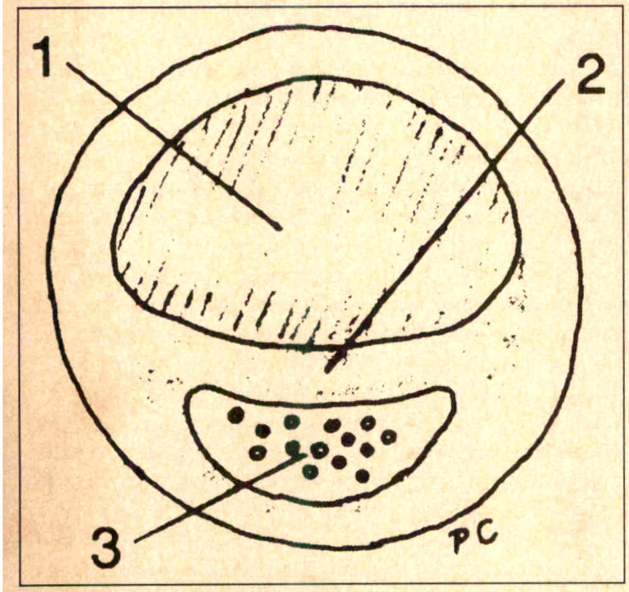

FIGURE 1. Typically, a thrombus (*1*) in an atherosclerotic coronary and other small arteries develops over a plaque with a seemingly intact fibrous cap (*2*) that very frequently overlies a hemorrhagic lipid gruel core (*3*). Note that the atheroma cap is "ironed out" by the blood pressure so that the arterial lumen, although stenosed, is still circular. (Adapted from Ultrastructural Pathobiology.[16])

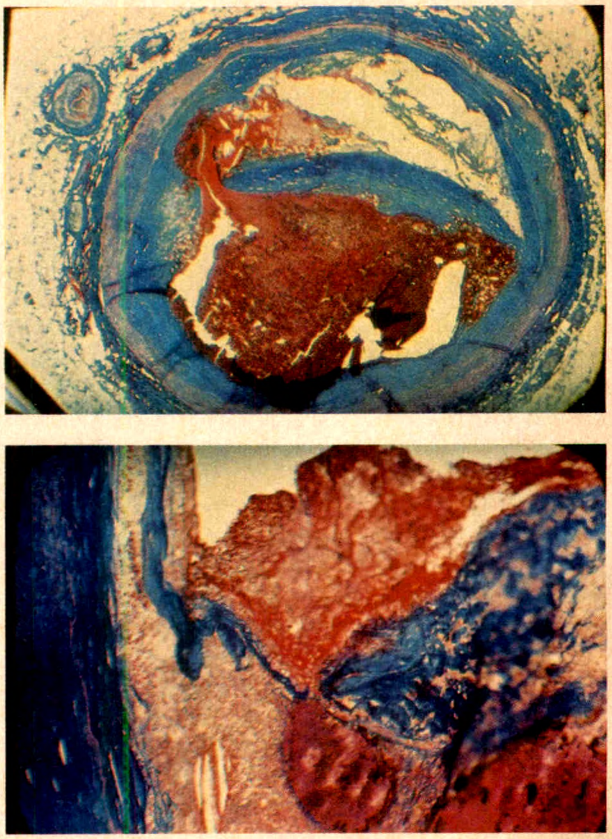

FIGURE 2. *A (top).* Section through a thrombosed atherosclerotic coronary in which collagen is stained blue, thrombus and blood various shades of red and what remains of the media, pink. The thrombus was caused by a break in the cap of the underlying plaque at the point on the *left* where the cap joins the rest of the wall (a frequent fissure site, presumably because of its mechanical vulnerability). Some blood entered the plaque interior through the break before it was sealed by the thrombus. *B (bottom).* Thrombosis in an atherosclerotic coronary artery, illustrating how small a thrombus-producing break can be and that it does not always lead to hemorrhage. This mural (nonocclucing) thrombus developed over a very small fissure (about 3 red cells, or 20 μ wide) at the point where the thin part joins the thick part of the blue collagenic cap, and a large round purple mass of platelets accumulated directly underneath the fissure, instead of a hemorrhage. (Adapted from *J Atheroscler Res.*[4])

Evidently, the next important question is, what causes these breaks? We do not know the answer yet, but present evidence suggests that any of the following mechanisms could trigger the fissuring of an advanced atheroma cap and therefore deserves to be further explored: (1) a pressure surge in the lumen, due to either a burst of systemic hypertension or a local arterial spasm distal to the plaque. This could stretch the arterial wall and crack it in its most unyielding, fragile area, i.e., the surface (cap) of the plaque (Fig. 3B); and (2) any influence that could weaken the structure of the atheroma cap and make it more fragile so that it could be broken more easily by an intraluminal pressure increase, or even break spontaneously. All processes that attack the endothelial lining, the smooth muscle cells that produce and maintain the collagen of the cap or the collagen of the cap itself fall under this heading, and especially the following: (a) metabolic or chemical insults (e.g., conditions that open the interendothelial junctions or damage endothelial cells such as prolonged hyperlipemia,[11] high plasma angiotensin levels,[12] high plasma acetoacetic acid concentrations at levels that occur in untreated diabetes[13] or nicotine);[14] (b) circulating immune complexes born elsewhere in the body that can penetrate into plaque surfaces (because of the increased permeability of plaque endothelium) where they could activate complement and kill cap cells;[15] (c) calcification of the matrix around the myocytes of the cap that buries these cells in stony caves and kills them by asphyxia, just as chondrocytes are killed in calcifying cartilage;[16] and (d) gradual molecular changes of cap collagen with time (e.g., increasing cross-linking that makes it more and more fragile so that one day it can be fissured by a very slight blood pressure surge—or even by a normal pulse wave, or the gradual contraction of collagen that could fissure it in the same manner in which cracks are produced in drying mud).

Finally, we must consider the possible role that 2 types of capillary hemorrhages could play in promoting breaks of atheroma caps: (1) the hemorrhages from the branches of the vasa vasorum that most frequently invade the base of advanced atheromata from the adventitia once the media, the barrier between them and the plaque interior, has been greatly thinned or destroyed, and (2) the hemorrhages from the capillaries that less frequently invade the atheroma from the lumen.

We shall first discuss the vasa vasorum (adventitial capillary) hemorrhages because recently certain investigators have hypothesized on purely hemodynamic grounds that most plaque hemorrhages may be caused by the rupture of the adventitia-derived capillaries, and that perhaps these capillary hemorrhages "blow" the atheroma from inside, breaking its cap and leading to a flow of blood from the plaque interior into the arterial lumen.[17]

We believe that this scenario could occur occasionally in some rare instances, but that it is not the common one because it is difficult to reconcile with hard histologic evidence in this area, for 5 reasons: (1) The great majority of the thrombogenic cap breaks in our complete serial section study (that yielded a thorough 3-dimensional reconstruction of the entire thrombosed arterial segment) occurred unequivocally in avascular plaque areas (i.e., in areas with no capillaries either at the break sites or proximal or distal to them); therefore, the breaks occurred without the help of any capillary hemorrhages. (2) In a minority of our cases (4 of 30), thrombi developed over breaks of caps without any hemorrhages whatsoever under the breaks, indicating that sometimes cracks can be sealed by thrombi before any blood can enter from the lumen into the plaque (perhaps due to a very slow cracking process, superactive thrombogenesis, or both). Again, this finding showed that the primary thrombogenic event is a break of the cap and that the hemorrhage is a secondary result that sometimes does not happen. (3) In the majority of our cases (26 of 30), in which the cracks were

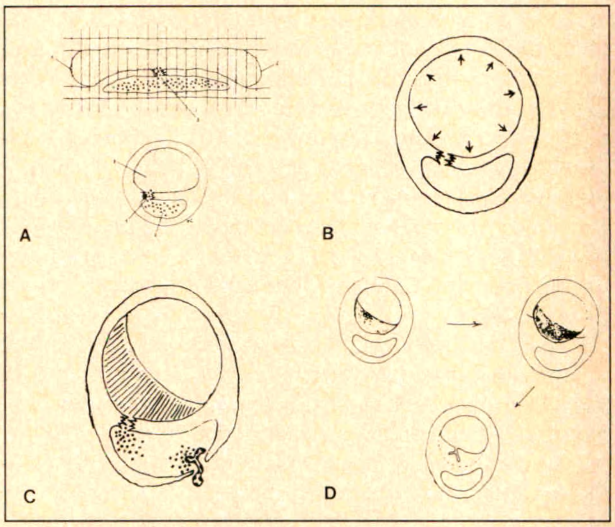

FIGURE 3. ***A, top,*** **a longitudinal section through a thrombosed coronary artery in which a long occlusive thrombus developed over an atheroma with a tiny break of its cap through which blood had poured into the plaque interior, spreading proximally and distally to the site of the break. Out of numerous serial sections from 1 end of a thrombus to another, only the few that run through the break area can reveal the break that caused both hemorrhage and thrombus, as shown in the** ***bottom.*** **All the other sections will show a thrombus formed over a seemingly intact atheroma cap with a hemorrhage in the underlying gruel, as in Figure 1.** ***B,*** **a sudden increase in pressure within a lumen can fissure the cap of an advanced atheroma, particularly if it has been structurally weakened by other chronic insults, including toxic degradation products from the lipid gruel underneath it.** ***C,*** **when a lumen-derived hemorrhage that fans out of a cap fissure under a thrombus coexists with a hemorrhage from branches of vasa vasorum that invade the atheroma from the adventitia, no physical connection between the 2 bleedings is usually seen—an indication of the different origins of the 2 bleedings.** ***D,*** **capillarization from the lumen begins with the development of a mural (nonocclusive) thrombus over the collagenic cap of an atheroma, as shown in the** ***top left.*** **The thrombus surface is then overgrown by endothelium that moves in from both sides and dips into the thrombus substance to form endothelial tubes, as shown in the** ***top right.*** **When the thrombus is completely organized and replaced by collagenic tissue (like that of the underlying cap), the end result is an atheroma with a much thicker cap that is capillarized from the lumen, as shown in the** ***bottom.*** **The process also illustrates the mechanism through which mural thrombosis promotes the growth of preestablished plaques. (Adapted from Ultrastructural Pathobiology.[16])**

associated with major hemorrhages, the latter had clearly resulted from the entry of blood from the lumen into the plaque before the breaks were sealed; the hemorrhages were fanning out from the cracks into the plaque interior; the cap fissures were beyond any doubt the "epicenters" of the bleedings. This was also the experience in the 5 other step-serial studies that confirmed our original results.[6-10] (4) In 4 of our 26 patients with major crack-induced hemorrhages we also saw some minor hemorrhages that originated unquestionably from the rupture of adventitia-derived capillaries in the deep portions of the plaques, but the latter had no physical connection with the former (Fig. 3C). It is interesting that in one of the recent step-serial reinvestigations of thrombosed coronary arteries, minor adventitial capillary-derived hemorrhages in the deep plaque regions were found to accompany the major lumen-derived hemorrhages in most cases, but, as in our own studies, no physical connection between the two types of bleeding was seen.[9] And (5) contrary to prevailing impressions, we found in our studies that most thrombi develop in only slightly or moderately stenosed coronary arteries; therefore, the Bernoulli principle (that would create suction in an extremely stenosed lumen) does not seem likely to operate as a primary cause of capillary and cap rupture in most cases of arterial thrombosis.

Thus, while our own histologic findings, and those of others, show that vasa vasorum-derived hemorrhages do not usually cause the thrombogenic cap breaks, they indicate that these capillary bleedings can coexist with the main lumen-derived hemorrhages in a variable percentage of thrombosed atherosclerotic arteries. Is this because in some cases the same agents—physical or chemical—that injure the plaque surface, causing a thrombogenic break, also injure the endothelium of adventitial capillaries? Is it because capillary hemorrhages—especially when they are protracted, extensive or repeated—can damage the cap tissue and make it more vulnerable to all the physical and chemical cap-fissuring factors we listed earlier? These and other possibilities could be easily explored in the intermittent hyperlipemia rabbit models in which in a little over 1 year extensive capillarizations from the adventitia develop in their highly advanced end-stage lesions.[2]

We must now briefly discuss the role of the hemorrhages from the less frequently encountered lumen-derived capillaries (the exact reverse of the vasa vasorum capillary bleedings), which about 50 years ago had been thought to be the possible initiators of coronary thrombosis.[1] Capillarization of plaques from the lumen does occur when the upper part of an atheroma cap is derived from the organization and incorporation of a supraplaque mural thrombus (Fig 3D). In fact, we did find and document, in our own serial-section study, several instances of lumen-derived capillaries and their hemorrhages, but none of them was associated with a cap break or thrombosis,[4] an experience shared with subsequent investigators of this problem.[6-10] However, it is conceivable that in some cases extensive luminal capillarization could make the cap very spongy and therefore more fragile, or that repeated or excessive hemorrhages from lumen-derived capillaries could, like those from adventitial capillaries, damage the cap and make it more vulnerable to other insults.

In conclusion, since plaques are very complex structures with many components that can be influenced by many different forces, it is likely that the thrombogenic breaks of their surfaces can be caused not just by 1 but by several different factors that often act in synergy. In the future, considerable progress might be achieved by the exploration of these factors in experimental models of advanced atherosclerosis that are now available.

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Rupture of Coronary Vasa Vasorum as a Trigger of Acute Myocardial Infarction

A. Clifford Barger, MD, and Reinier Beeuwkes, III, PhD

Some controversy has always existed regarding the presence and extent of the vasa vasorum—the nutrient vessels in the wall of the human aorta—in the coronary arteries. Now, cinemicrographic studies using silicone polymer injections in cleared human hearts have identified the vasa vasorum of coronary arteries, revealing evidence of neovascularization in the region of atherosclerotic plaques. These studies suggest an important role for the vasa vasorum in the pathogenesis of coronary atherosclerosis and its sequelae, especially intramural hemorrhage and vascular spasm. The wall of the human coronary artery in regions of atherosclerotic injury may be particularly rich in capillary vessels of the vasa vasorum. From this, the evidence suggests that with the morning increase in blood pressure, fragile neovascular structures of the vasa vasorum may be more prone to rupture and may be responsible, in part, for the circadian variation in myocardial infarction.

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Rupture of the coronary vasa vasorum may play an important role in the onset or triggering of myocardial infarction (MI). Although these "vessels of the vessels" in the heart are infrequently described and little understood, new evidence suggests that there is extensive neovascularization of intramural atherosclerotic plaques.[1–4] This dense plexus of microvessels (Fig. 1) may be implicated in the deposition of blood products in the walls of coronary arteries[1,5,6] despite the presence of intact coronary endothelium.

By cinemicrographic studies of cleared human hearts we have demonstrated that the direction of flow in these fragile vessels is inward from the adventitial vasa vasorum through the media into the thickened intima, rather than outward from the coronary lumen.[2]

In addition, microsphere studies have shown that vasa vasorum blood flow in the region of atherosclerotic plaque is increased fivefold over that observed in the normal media.[7] The increased blood flow implies a large inward (lumen-directed) pressure gradient in the stenosed region of the coronary artery (Fig. 2). This is not surprising because luminal blood flow creates a region of low pressure centered in the narrowest point of the stenosis (the Bernoulli principle),[8–10] while the vasa vasorum arise upstream in a high-pressure region. Thus, the vascularity of plaques, the fragility of mural vessels and mural pressure gradients may better predict the site of a future MI than degree of coronary artery narrowing alone.

METHODS

Over 100 human hearts were obtained at autopsy from male and female patients ranging in age from 19 to 96 years. The hearts were fixed by pressure perfusion of the coronary arteries with 2% glutaraldehyde, dehydrated in increasing concentrations of ethanol and cleared in methyl salicylate, rendering the epicardial fat and blood vessel walls transparent. To show the vascular and microvascular structures, a low-viscosity, white silicone polymer (MV 112, Canton Biomedical Products) was injected into the cleared vessels, and the flow pattern of the injection was filmed with a special optical system.

RESULTS

Motion picture records clearly documented not only the filling of the major coronary arteries, but also showed, for the first time, the direction of flow in the microvascular network of the intramural vasa vasorum. Films of the normal region of the arteries showed only a sparse, linear, adventitial pattern of vasa vasorum, whereas a dense capillary network of neovascular appearance was noted in atherosclerotic plaque regions (Fig. 1). This network

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arose from more proximal branches of the coronary arteries, traversed the adventitia and media and flowed toward the thickened intima.

Of the hundreds of plaques examined, no case was observed in which flow occurred from the coronary lumen into the local mural network of the plaque. Histologic examination of tissue taken from the photographed regions verified the presence of vasa vasorum in the adventitia, media and intima of plaque regions and demonstrated a quantitative relation between the degree of neovascularization as measured by micrography and the histologic examination.[3]

DISCUSSION

These cinemicrographic and histologic studies strongly suggest that rupture of the vasa vasorum in the wall of the atherosclerotic coronary artery may trigger onset of an MI, a view that has received support from the recent work of Cuénoud and Chung[5] and Maher and Cuénoud.[6] Many pathologists, however, are of the opinion that "the relatively tremendous pressure from the lumen"[11] in the region of the stenosis induces plaque fissuring, with hemorrhages into the wall.

Such a view would be at variance with the Bernoulli principle and the evidence provided by recent theoretical and experimental hemodynamic studies.[9,10] Indeed, if local coronary luminal pressure was much greater than that in the vasa vasorum, then we would expect these small vessels to be compressed, not open and flowing rapidly as shown by Heistad and Armstrong.[7]

Moreover, Little et al[12] reported in 1988 that the degree of narrowing of the coronary arteries as visualized by angiography may not predict the site of a subsequent MI in patients with coronary artery disease. These findings implicate factors other than the size of the atherosclerotic stenosis per se.

CONCLUSION

More than 25 years ago Paterson[13] wrote: "Severe grades of coronary atherosclerosis may exist in man without the production either of pathologic sequelae or clinical signs or symptoms. And it is equally certain that, more or less suddenly, such severe lesions may become clinically apparent with the development of angina pectoris, ventricular fibrillation with sudden death, and/or myocardial infarction .... When an intimal defect is seen in association with hemorrhage it should be interpreted as a 'blow-in' into the lumen, not as a 'blow-out' from the lumen .... Because intimal hemorrhage can be demonstrated so well in coronary arteries without thrombosis, it cannot be regarded as a secondary intimal change resulting from the pressure of an occluding mass in the lumen."

We may conclude, therefore, that with the morning increase in blood pressure, the fragile neovascular structures of the vasa vasorum may be more prone to rupture. Such rupture may, in part, be responsible for the circadian variation in MI that has been described by Muller et al.[14]

Addendum: "Plaque and vasa vasorum in human coronary arteries," motion picture film number 22710, on which much of this report is based, is available for loan from Hoechst-Roussel Film Library, Modern Talking Picture Service, 5000 Park Street North, Saint Petersburg, Florida 33709.

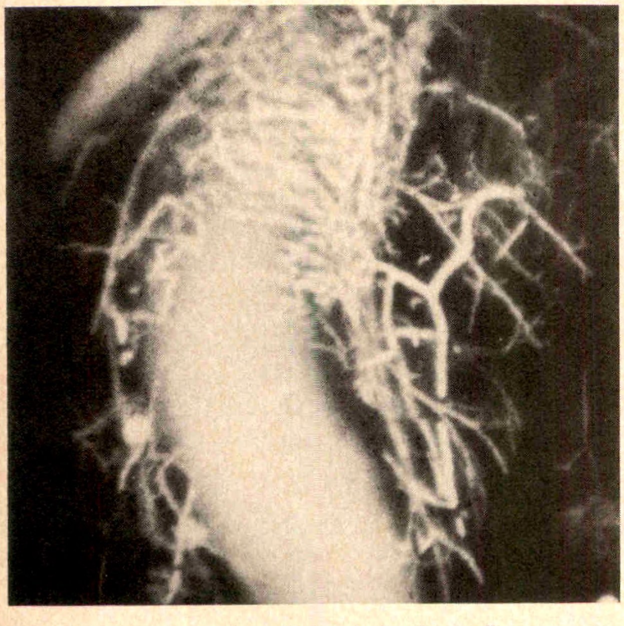

FIGURE 1. Vasa vasorum of left anterior descending coronary artery (human heart). Note the dense neovascular network in the atherosclerotic plaque (*upper portion of artery*). Only a few such vessels are seen in the normal region (*lower portion*).

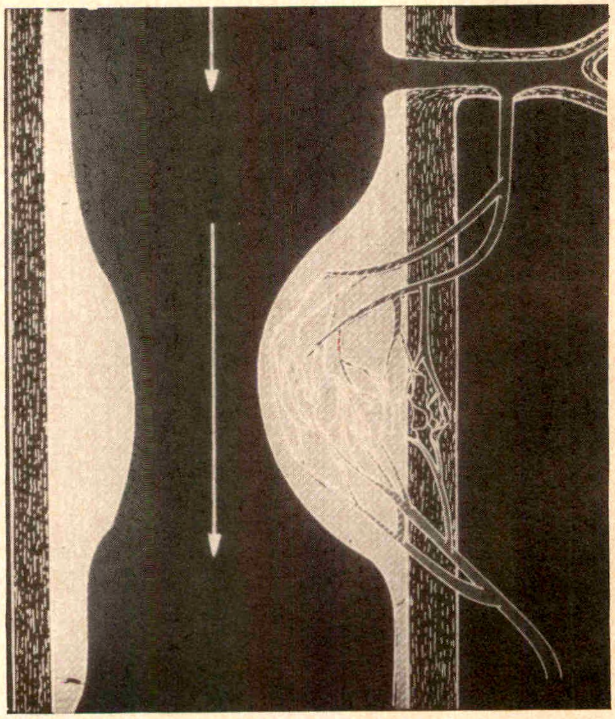

FIGURE 2. Diagrammatic illustration of flow pattern in the vasa vasorum of the atherosclerotic plaque. Note that the vasa vasorum arise in a high-pressure zone above the plaque.

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Angiographic Assessment of the Culprit Coronary Artery Lesion Before Acute Myocardial Infarction

William C. Little, MD

Serial angiographic studies of patients with myocardial infarction and unstable angina suggest that the culprit plaque underlying a thrombus need not have produced severe luminal obstruction before onset of the event. An atherosclerotic coronary artery lesion can, therefore, have 2 important characteristics. First, it may be obstructive. Second, it may be "vulnerable" in that it has the potential to become thrombogenic if exposed to the appropriate triggering stimulus. A lesion need not be obstructive to become thrombogenic, nor do all obstructive lesions have thrombogenic potential. The cause of an infarction may thus be rupture of a nonobstructive plaque leading to occlusive thrombus formation.

Because it may be difficult to predict the site of a subsequent occlusion from a coronary angiogram, coronary bypass surgery or angioplasty directed only at discernible stenotic lesions may not be effective for preventing subsequent myocardial infarctions. Appropriate therapy may need to be directed at the entire coronary tree. Such therapy might include cholesterol lowering, β blockade and aspirin.

(Am J Cardiol 1990;66:44G–47G)

Myocardial infarction (MI) is usually caused by sudden thrombotic occlusion of a coronary artery at the site of an atherosclerotic plaque.[1] The formation of the occlusive thrombus is thought to result from rupture or cracking of the atherosclerotic lesion, which exposes thrombogenic plaque components to the bloodstream.[2] It is important in the management of patients with coronary artery disease (CAD) to understand the characteristics of coronary artery lesions that have the potential to produce thrombotic occlusions.

Coronary angiography is the standard clinical tool for evaluating patients with suspected CAD. Prognosis is inversely related to the number of stenotic coronary vessels.[3] High-grade stenosis (>80% diameter narrowing) and extensive CAD correlate with a higher risk for subsequent occlusion.[4] Stenotic areas are frequently assumed to represent possible sites for future thrombotic occlusion, whereas arterial segments that do not contain stenoses are presumed to be relatively risk free. Recent findings, however, suggest that an obstructive coronary artery lesion is not necessary for the development of a thrombotic coronary artery occlusion producing a MI.

SERIAL ANGIOGRAPHIC STUDIES

We recently evaluated coronary angiograms of 29 medically treated patients with CAD who had undergone angiography before and after MI.[5] The second angiogram was used to determine the location of the infarct-producing obstruction, and the first angiogram was studied to assess the coronary anatomy preceding the MI. On the initial angiograms, taken 4 to 2,298 days before MI, most patients (83%) exhibited 1- or 2-vessel disease; yet in only 34% of patients was the previously patent artery with the most severe stenosis responsible for the MI. Frequently, the artery that subsequently occluded had not exhibited a high-grade angiographic stenosis before MI (Fig. 1). In fact, preexisting luminal diameter narrowing was <50% in 66% (19) of these patients, and minimal luminal diameter was >1 mm before infarction in 90%.

Ambrose et al[6] recently performed a similar analysis of 23 patients who had undergone serial coronary angiograms before and after MI, with nearly identical results. Only 22% of infarct-related arteries had been identified as having >70% diameter stenosis before MI. Both studies suggest that the culprit coronary artery lesion need not have been severely stenotic before MI.

Ambrose et al observed that patients who suffered non-Q-wave MI, or who did not experience MI despite coronary occlusion, had more severe preexisting stenoses

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than patients with Q-wave MI. By contrast, we found no differences in the severity of preexisting coronary stenosis between patients with non-Q-wave or Q-wave MI.[7] It is possible that in some patients, severe preexisting stenosis stimulates collateral development, thus limiting or preventing myocardial necrosis after thrombotic occlusion.

Patients not included in either the study of Ambrose et al[6] or in our study[5] were those who underwent coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) after the initial angiogram—comprising a group who probably had the most severe CAD. To help overcome the potential bias of this omission, we have recently evaluated a group of patients who had suffered MI a month or more after successful CABG or PTCA.[8,9] Coronary angiography performed within 2 weeks of MI was used to define the infarct-related artery. The angiogram obtained before CABG or at the time of PTCA was used to assess the preexisting CAD. We found that 33% of the MIs after successful CABG were due to occlusion of an artery that had not been bypassed.[8] The infarct-producing artery had not received a bypass graft because, in all patients except 1, it had not contained an obstructive (>50%) stenosis. Similarly, 57% of MIs after successful PTCA were due to occlusion of an artery that had not been dilated because it did not contain an obstructive stenosis at that time.[9]

Previous studies by Moise et al[4] and Singh[10] of patients undergoing serial coronary angiograms also provide information on the severity of the culprit lesion before MI. In these studies, patients were not limited to those recently suffering an acute MI, as in our study. Moise et al,[4] in their review of 313 patients who had undergone 2 coronary angiograms for any reason, report finding 116 newly occluded coronary vessels at the second angiogram. The presence of high-grade (>80%) coronary stenosis, the extent of CAD, cigarette smoking and male sex were factors most predictive of a new coronary artery occlusion. Thus, Moise et al[4] concluded that coronary angiography combined with 2 clinical factors could predict MI. Analysis of the data from Moise et al,[4] however, indicates that 72% of occlusions in this study occurred in segments that previously contained <75% stenosis.

Similarly, Singh[10] studied 52 patients who underwent serial coronary angiograms for any reason and found that 12 of the 25 new total occlusions present in the second angiogram occurred in segments that had been free from stenosis 2 to 108 months earlier. From these and other studies we conclude that although coronary artery segments that contain high-grade obstruction are at risk for occlusion,[11] many occlusions occur in arteries that did not previously contain a high-grade stenosis.

STUDIES DURING THROMBOLYTIC THERAPY

Occasionally, angiographically normal coronary arteries are seen in patients after MI.[12] Presumably the occluding thrombus has spontaneously lysed before angiography, suggesting that angiographically normal arteries may occasionally thrombose, although it is possible that in some cases the infarction was caused by coronary artery spasm. After MI, when coronary blood flow has been restored by thrombolytic therapy, a high-grade residual stenosis frequently remains.[13] This may indicate that the atheroma at the site of coronary occlusion was obstructive and should have been easily identified by coronary angiography before the event. Alternatively, residual thrombi may overlie the atheroma, making the lesion appear much more severe than it was immediately before the infarct. The study of Brown et al[14] suggests the latter possibility is most common. They used angiographic magnification and computerized measurements to separate the atheroma from the overlying thrombus in 32 patients who had received intracoronary streptokinase. The underlying atherosclerotic lesion responsible for producing the MI was not severe in most patients and on average produced only a 56% stenosis.

OTHER DATA

Other studies provide indirect evidence consistent with the hypothesis that a coronary atheroma need not be recognizable as an obstructive stenosis on coronary angiography to subsequently be responsible for an infarction. First, many patients suffer MI without having previously experienced exertional angina.[15,16] In many of these patients, the coronary arteries may not have contained obstructive lesions before MI.

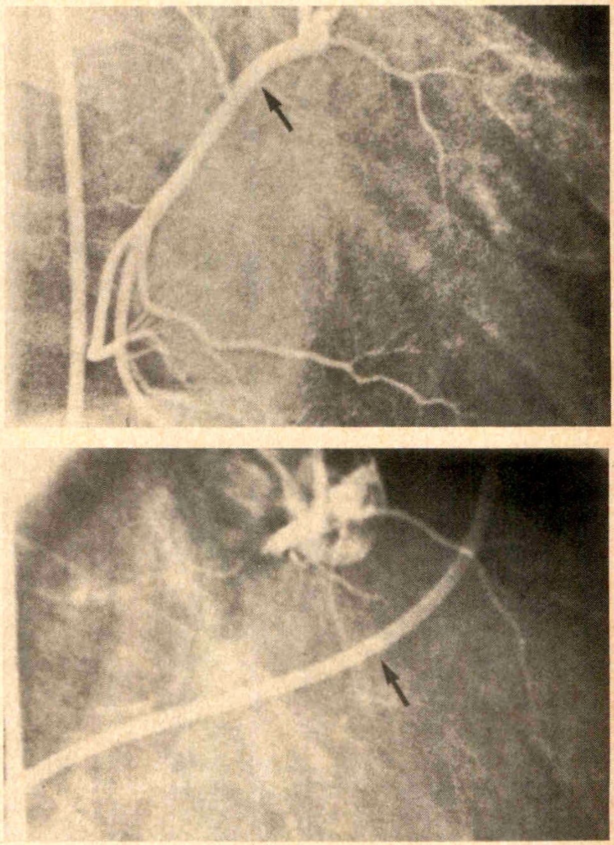

FIGURE 1. Angiograms of the right coronary artery taken 9 months before (*top*) and immediately after (*bottom*) the patient suffered an acute inferior myocardial infarction (MI). Note absence of obstructive stenosis in the infarct-related artery before MI.

Second, it is now apparent that the pathogenesis of unstable angina may be similar to that of acute MI, in that a thrombus overlying an atheroma has obstructed, but not occluded, blood flow.[17] In agreement with results of serial angiography of patients with MI, the artery responsible for unstable angina frequently does not contain a high-grade stenosis before the development of unstable angina.[18,19]

Finally, coronary angiography may fail to reveal the extent of atherosclerosis.[20] Although only discrete areas of stenosis may be evident on angiography, the atherosclerotic process may be much more diffuse. For example, endothelial function in areas without signs of obstruction may be abnormal.[21] Lack of apparent stenosis in an arterial segment does not necessarily indicate that the segment is free from atherosclerosis, particularly if stenotic lesions are present elsewhere in the coronary arteries.

ANGIOGRAPHIC MORPHOLOGY OF CULPRIT LESIONS

The endothelium of the culprit plaque underlying coronary thrombosis in patients with MI or unstable angina generally has been disrupted, so that blood in the lumen is exposed to thrombogenic plaque components. This plaque disruption may appear angiographically as a convex intraluminal obstruction with overhanging edges, irregularities, intraluminal defects, or a combination of these.[22,23] Culprit plaques frequently have these characteristics after the development of MI or unstable angina.[24,25] How frequently they exist before MI is unknown. It is possible that stenoses with these characteristics in patients without MI may have a high risk for subsequent occlusion.[26]

CONCLUSIONS

Serial angiographic studies of patients with MI[5,6] suggest that the culprit plaque underlying a thrombus need not have produced severe luminal obstruction before the event. This conclusion is consistent with both the frequent occurrence of MI without preceding angina[15,16] and also with serial angiographic studies of patients with unstable angina.[18,19]

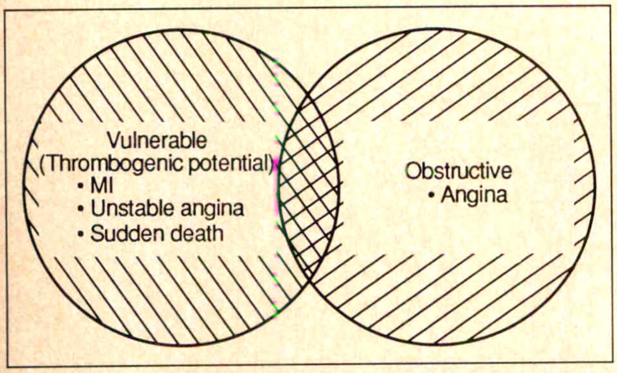

FIGURE 2. The clinically important characteristics of coronary artery atherosclerotic lesions. The plaque can be obstructive or vulnerable (i.e., have thrombogenic potential), or both. Obstructive plaques produce angina. If a vulnerable plaque is exposed to the appropriate triggering stimuli, it may produce thrombus formation resulting in myocardial infarction (MI), unstable angina or sudden death. Not all vulnerable plaques are obstructive, and not all obstructive plaques are vulnerable.

Based on these data, we propose that the atherosclerotic coronary artery lesion can have 2 important characteristics (Fig. 2). First, it may be obstructive. Such lesions can be recognized on coronary angiograms, and they may produce exertional angina. Second, plaques may be "vulnerable," in that they have the potential to become thrombogenic if exposed to the appropriate triggering stimuli.[27] Such plaques, if they express their thrombogenic potential, may cause an infarction or sudden death[28] if the resulting thrombus occludes the coronary artery, or produce unstable angina if the thrombus obstructs but does not occlude the artery. As shown in Figure 2, a stenosis need not be obstructive to become thrombogenic, nor do all obstructive lesions have thrombogenic potential.

The presence of angiographic evidence of obstructive stenosis indicates that a patient has coronary atherosclerosis and the potential for MI, but the coronary stenosis does not necessarily represent the location at which the thrombotic occlusion will occur. Because the prognosis for patients with stable angina is related to the number of stenosed coronary arteries,[3] it is possible that the potential for thrombogenic lesions increases with the number of obstructive lesions. However, that does not mean that all potentially thrombogenic lesions will produce angiographically apparent obstruction or angina.

Because it may be difficult to predict the site of a subsequent occlusion from an initial coronary angiogram, coronary bypass surgery or angioplasty directed only at discernible lesions may not be effective for preventing subsequent MI. This does not imply that arteries free from obstructive lesions should be bypassed or dilated. Instead, therapy to prevent MI may need to be directed at the entire coronary tree, not just the obstructive lesions. Such systemic therapy to prevent MI might rationally include reducing serum cholesterol levels in an effort to slow the development of vulnerable lesions; minimizing potential triggers of plaque disruption by avoiding smoking, and, possibly, administering β blockers; and altering platelet function with aspirin.

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Potential Usefulness of Combined Thromboxane A_2 and Serotonin Receptor Blockade for Preventing the Conversion from Chronic to Acute Coronary Artery Disease Syndromes

James T. Willerson, MD, Paolo Golino, MD, John Eidt, MD,
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Evidence suggests that unstable angina, non-Q-wave myocardial infarction and Q-wave myocardial infarcts represent a continuum, such that transient reduction in coronary blood flow associated with platelet aggregation and dynamic vasoconstriction at sites of coronary artery stenosis and endothelial injury lead to abrupt development of unstable angina. Factors potentially responsible for the conversion from chronic to acute coronary artery disease include endothelial injury at sites of stenosis. The endothelial injury may be the result of plaque fissuring or ulceration, hemodynamic factors (including systemic arterial hypertension or flow shear stress), infection, smoking, coronary arteriography or balloon angioplasty. Clinical and experimental animal studies suggest that interference with thromboxane and serotonin contributions to platelet aggregation and dynamic coronary artery constriction may prevent chronic coronary artery disease syndromes from converting to acute disease. To protect against this process may require both thromboxane and serotonin receptor antagonists or a combination of thromboxane synthesis inhibitor and receptor antagonist with a serotonin receptor antagonist. Further studies are needed to test this hypothesis.

(Am J Cardiol 1990;66:48G–53G)

Acute coronary artery disease syndromes, including unstable angina and acute myocardial infarction, are usually caused by a primary decrease in myocardial oxygen delivery.[1–15] Unstable angina occurs in some patients with endothelial injury or ulceration at the site of a coronary artery stenosis,[6] and some patients develop intraluminal coronary artery thromboses.[4–6,9–11] Falk[7] and Davies and Thomas[8] have suggested that atherosclerotic plaque rupture or fissuring may lead to coronary arterial thrombi and the development of unstable angina, acute myocardial infarction or sudden death.[7,8] Patients with Q-wave (usually transmural) myocardial infarcts often have ulcerated or fissured atherosclerotic plaques and the subsequent development of occlusive coronary artery thrombi.[2,3] Patients with non-Q-wave infarcts much less commonly have completely occlusive coronary artery thrombi,[3] but these patients do have transient reductions in oxygen delivery to the myocardium followed by reperfusion.[16]

We have suggested that the transient reductions in coronary blood flow occurring in these clinical syndromes may be caused by intermittent platelet aggregation and dynamic vasoconstriction occurring at sites of coronary artery stenosis and endothelial injury (Fig. 1).[4,5,17] We have also speculated that unstable angina, non-Q-wave myocardial infarction and Q-wave myocardial infarcts represent a continuum, such that transient reductions in coronary blood flow associated with platelet aggregation and dynamic vasoconstriction at sites of coronary artery stenosis and endothelial injury lead to the abrupt development of crescendo or unstable angina.[4,5,17] Finally, we have suggested that if important reductions in coronary blood flow and oxygen delivery are sustained for 20 minutes to 1 to 2 hours, a non-Q-wave myocardial infarction may occur and, if the period of important reduction in myocardial oxygen delivery persists for more than 2 hours, a Q-wave infarct may develop.[4,5,17] In this suggested pathophysiologic scheme, potential factors responsible for the conversion from chronic to acute coronary artery disease syndromes include endothelial injury at sites of coronary artery stenosis.[4,5,17] The endothelial injury may result from plaque fissuring or ulceration,[7,8] hemodynamic factors (including systemic arterial hypertension or flow shear stress), infection, smoking, coronary arteriography or balloon angioplasty.

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TABLE I Potential Causes of Unstable Angina Pectoris

Progressive coronary artery narrowing from atherosclerosis
Platelet aggregation and white blood cell adhesion and platelet and/or white blood cell-derived mediator release at the site of endothelial injury and coronary artery stenosis leading to increased luminal narrowing from anatomic obstruction and increases in coronary vascular resistance
Any combination of plaque fissure, hemorrhage or thrombosis with progressive coronary artery narrowing
Coronary artery spasm

Platelets attach to the exposed subendothelium and collagen after endothelial injury to an artery. Platelet aggregation leads to the release and local accumulation of thromboxane A_2 and serotonin, which may promote further platelet aggregation and dynamic coronary artery vasoconstriction with consequent reductions in coronary blood flow (Fig. 1).[4,5,10-14,17-29] The dynamic coronary artery vasoconstriction and platelet aggregation are almost certainly contributed to by relative or absolute decreases in local arterial concentrations of endothelially derived vasodilators and inhibitors of platelet aggregation, including endothelially derived relaxing factors (EDRFs) and prostacyclin (Fig. 1).[5,17,21,30]

We believe that chronic endothelial injury at sites of coronary artery stenosis lasting days to weeks is associated with the accumulation of platelets and white and red blood cells in a fibrin mesh. Coronary artery thrombosis and dynamic vasoconstriction developing with more chronic endothelial injury may be associated with the accumulation of other mediators, including platelet-activating factor, selected leukotrienes (LTC_4 and LTD_4), thrombin, adenosine diphosphate, histamine, prostaglandin D_2 and, possibly, endothelin.[4,5,16,17,31]

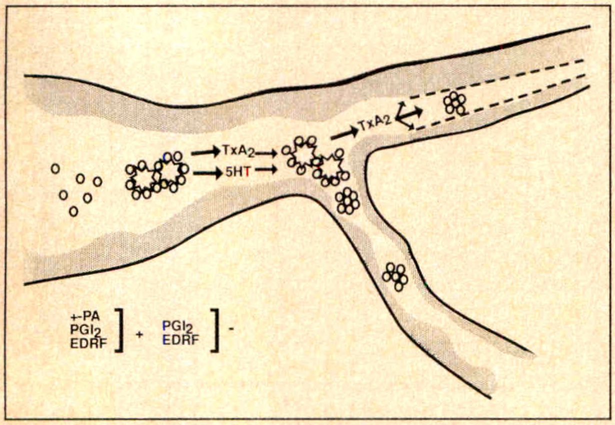

FIGURE 1. A schematic diagram indicating the possible mechanisms by which thromboxane A_2 (T_xA_2) and serotonin promote platelet aggregation and decrease coronary blood flow in the patient with unstable angina. Aggregating platelets (*stars*) release thromboxane A_2 and serotonin at sites of coronary artery stenosis and endothelial injury, which cause further platelet aggregation at that site and downstream, dynamic coronary vasoconstriction and partial or total coronary artery thrombosis. The absence or reduction in endothelially derived relaxing factor and prostacyclin at vascular sites with endothelial injury probably contributes to the development of vasoconstriction and thrombosis. EDRF = endothelially derived relaxing factor; 5HT = serotonin; PA = platelet aggregation; PGI_2 = prostacyclin. (Adapted from *Circulation.*[17])

UNSTABLE ANGINA

Unstable angina pectoris is defined as angina that increases in frequency with progressively less effort, and it often occurs at rest. Any factor that results in abrupt or progressive coronary artery luminal-diameter narrowing may cause diminished myocardial perfusion, with consequent myocardial ischemia and unstable angina. Table I lists several possible causes of unstable angina. In some patients, the syndrome results from the progression of severe, multifocal coronary atherosclerosis, but for many others we believe that other mechanisms are involved

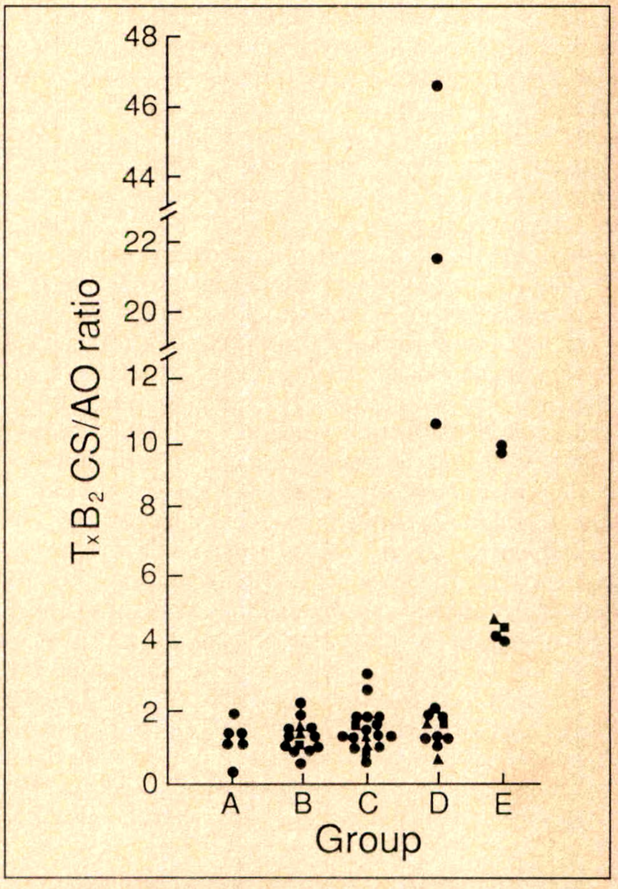

FIGURE 2. Ratios of thromboxane B_2 (T_xB_2) in the coronary sinus (CS) and ascending aorta (AO) in 5 groups of patients (n = 60). Each point represents data from 1 patient. *Squares* identify patients who received a cyclooxygenase inhibitor within 5 days of study, and *triangles* represent patients with coronary artery spasm. In groups A (valvular and congenital nonischemic heart disease), B (chest pain syndrome without ischemic heart disease) and C (ischemic heart disease without chest pain for at least 96 hours), the patients had thromboxane B_2 coronary sinus/aorta ratios of 3.1 or less. Group D patients (unstable angina pectoris with chest pain 24 to 96 hours before study) had a bimodal distribution: 12 patients had low ratios, whereas 3 had very high ratios. Group E patients (unstable angina pectoris with chest pain within 24 hours before study) had ratios that were higher than those of patients in groups A, B and C ($p < 0.05$). (Adapted from *N Engl J Med.*[10])

because often there is no good correlation between acute coronary artery disease and the anatomic extent and severity of coronary atherosclerosis.

CONVERSION FROM CHRONIC TO ACUTE CORONARY ARTERY DISEASE SYNDROMES

In 1979, and more recently, our group[10] hypothesized the following: (1) Increases in thromboxane and decreases in prostacyclin concentration at sites of endothelial injury and significant coronary artery stenosis cause platelet aggregation and dynamic coronary vasoconstriction that lead to the development or sustainment of unstable angina pectoris as a result of platelet aggregation or coronary vasoconstriction, or both, diminishing regional coronary blood flow below a critical level. (2) Mechanisms responsible for endothelial injury at sites of coronary artery stenosis vary, but probably include (a) progression, fissuring, or rupture of atherosclerotic plaques;[7,8] (b) hemodynamic factors, including flow turbulence; (c) cigarette smoking; (d) systemic arterial hypertension; (e) infection or immune complex deposition; and, on occasion, (f) catheter-induced endothelial injury associated with coronary arteriography and angioplasty.

The hypothesis that unstable angina is associated with increases in transmyocardial thromboxane A_2 concentrations was tested from 1979 to 1980.[10] In 60 patients undergoing cardiac catheterization, blood samples were obtained from the coronary sinus and ascending aorta, and prostaglandins were measured by radioimmunoassay.[10] By history, noninvasive evaluation and results of cardiac catheterization, patients were separated into 5 groups: group A patients ($n = 6$) had congenital and acquired noncoronary cardiac lesions, but were without significant coronary stenoses; group B patients ($n = 14$) complained of chest pain, but had no significant coronary artery stenoses or provocable coronary artery spasm; group C patients ($n = 18$) had significant coronary artery disease and their most recent episodes of chest pain occurred more than 96 hours before study; group D patients ($n = 15$) had chest pain that had occurred 24 to 96 hours before study; and group E patients ($n = 7$) had unstable angina with chest pain within 24 hours of study (Fig. 2).

Thromboxane B_2 (the inactive metabolite of thromboxane A_2) concentrations were elevated across the coronary bed in group E patients (i.e., those with continuing rest angina), and values in this group were significantly higher than those of patients in groups A, B and C. Group D patients had a bimodal distribution—12 patients had low thromboxane B_2 concentrations, and 3 had markedly elevated values. It is not clear why 3 patients in group D had elevated transcardiac concentrations of thromboxane B_2. However, possible explanations include persistent increases in transcardiac thromboxane concentration despite relief from unstable angina; and continuing unstable angina not detected clinically or identified by the patient (i.e., silent myocardial ischemia). We were unable to show differences in transmyocardial prostacyclin concentrations among these patients.[10]

These data demonstrate a temporal relation between continuing unstable angina and increases in transcardiac thromboxane concentrations. Results are consistent with the hypothesis that thromboxane A_2 accumulation and the consequent platelet aggregation and coronary vasoconstriction are important factors in the pathogenesis of unstable angina. However, a causal relation was not established.

Subsequently, Fitzgerald et al[11] (at Vanderbilt) and Hamm et al[12] demonstrated that many patients with unstable angina were found to have elevated urinary concentrations of a major thromboxane metabolite, 2-3 dinor-thromboxane B_2; for some patients, at least, additional episodes of chest pain resulted in even further increases.

PHYSIOLOGIC IMPORTANCE OF THROMBOXANE ACCUMULATION

In the canine heart, severe proximal coronary artery stenosis with associated endothelial injury causes cyclical coronary bloodflow reductions as originally described by Folts et al[18] (Fig. 3). In this model, endothelial injury is caused by the application of an external constrictor and gentle stroking of the left anterior descending artery with cloth-covered forceps. The cyclical coronary-flow alterations are related to platelet aggregation and leukocyte and red blood cell accumulation at the stenotic site. Da-

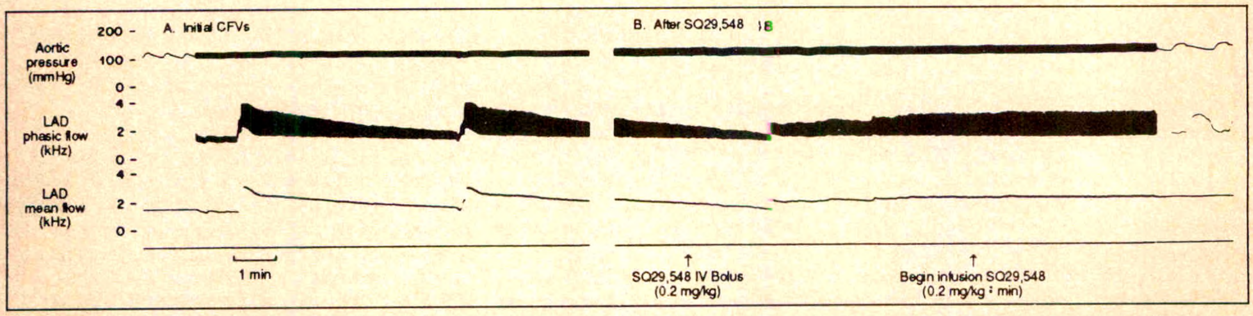

FIGURE 3. A representative recording for a dog with cyclic coronary flow variations and abolition of the cyclic flows with SQ29,548, a thromboxane receptor antagonist (Squibb Pharmaceuticals). *A*, Initial coronary flow variations. Note the recurring pattern of decline and restoration of mean and phasic left anterior descending coronary artery flow. *B*, A normal pattern of flow restored minutes after administration of SQ29,548. Cyclic coronary flow variations occur in the canine model with a tight proximal coronary artery stenosis and endothelial injury as previously reported.[18–27] CFV = coronary flow variation; IV = intravenous; LAD = left anterior descending coronary artery. (Adapted from *Circ Res*.[20])

zoxiben (UK-37-258, Pfizer Pharmaceuticals), a thromboxane synthetase inhibitor,[19] or SQ29,548 (Squibb Pharmaceuticals), a thromboxane receptor antagonist,[20] abolish or significantly attenuate the frequency of cyclic flow reductions in approximately 70% of treated animals (Fig. 3). Thromboxane B_2 concentrations in the distal portion of the narrowed coronary artery and at the site of the coronary stenosis and endothelial injury are increased during cyclic coronary flow reductions and reduced to control values after administration of dazoxiben.[19,21] In contrast, 6-keto-prostaglandin F_{1a} (the inactive metabolite of prostacyclin) generation is reduced at the site of coronary artery constriction but not in the nonconstricted, noninjured coronary artery.[21] Distal coronary artery 6-keto-prostaglandin F_{1a} levels increase significantly during cyclic flow reductions and remain elevated after the administration of dazoxiben.[19] Systemically administered dazoxiben (2.5 mg/kg body weight, intravenously) suppresses arachidonic acid-induced thromboxane A_2 (but not prostaglandin E_2) production by canine platelets, but it does not significantly influence prostacyclin synthesis by canine coronary artery rings.[19] Furthermore, the topical application or intraatrial administration of a thromboxane-mimetic (U46619) generally restores cyclic coronary flows in this model after they are abolished by a thromboxane-synthesis inhibitor.[19] Folts et al [18] have demonstrated that aspirin often eliminates cyclic coronary artery flow reductions in the same experimental model.

Therefore, thromboxane concentration increases at the site of a coronary artery stenosis and endothelial injury in the canine model, and the narrowed injured artery makes substantially more thromboxane when arachidonic acid is added in vitro.[19,21] The administration of a thromboxane synthetase inhibitor or receptor antagonist usually abolishes cyclic flow alterations in this model.[19-21] More recently, we have demonstrated that dynamic coronary vasoconstriction occurs adjacent to the site of stenosis in the canine model and that thromboxane and serotonin receptor antagonists prevent dynamic vasoconstriction.[22] Thromboxane synthesis inhibitors and receptor antagonists are also protective against in situ platelet aggregation[23] in this model.

THE ROLE OF SEROTONIN IN EXPERIMENTAL MODELS

We found that a thromboxane synthesis inhibitor or receptor antagonist was protective and abolished cyclical alteration in coronary blood flow in approximately 70% of the treated animals. Thus, it was apparent that another mediator (or mediators) contributes to the development of cyclical alterations in coronary blood flow in the canine model. More recently, we have shown that serotonin concentration increases by at least 18-fold at the site of a coronary artery stenosis and endothelial injury when cyclic coronary artery flow reductions occur.[24] Ketanserin, a serotonin receptor antagonist, usually abolishes cyclic flow reductions.[24,25] It works in essentially every instance in which a thromboxane synthetase inhibitor or receptor antagonist, or both, have failed (Fig. 4).[24,26] Other serotonin receptor antagonists, without α_1 adrenergic antagonist properties at the concentrations at which they were used, also abolish cyclic coronary flow alterations in approximately 90% of animals, and are effective when thromboxane synthetase inhibitors or receptor antagonists have failed.[26] After cyclic flows are abolished by serotonin receptor antagonists, they may be restored by the intraatrial administration of serotonin.[24] There is an amplification of thromboxane and serotonin's effects on cyclic coronary flow variations, such that interfering with the effect of either usually eliminates cyclic coronary flow

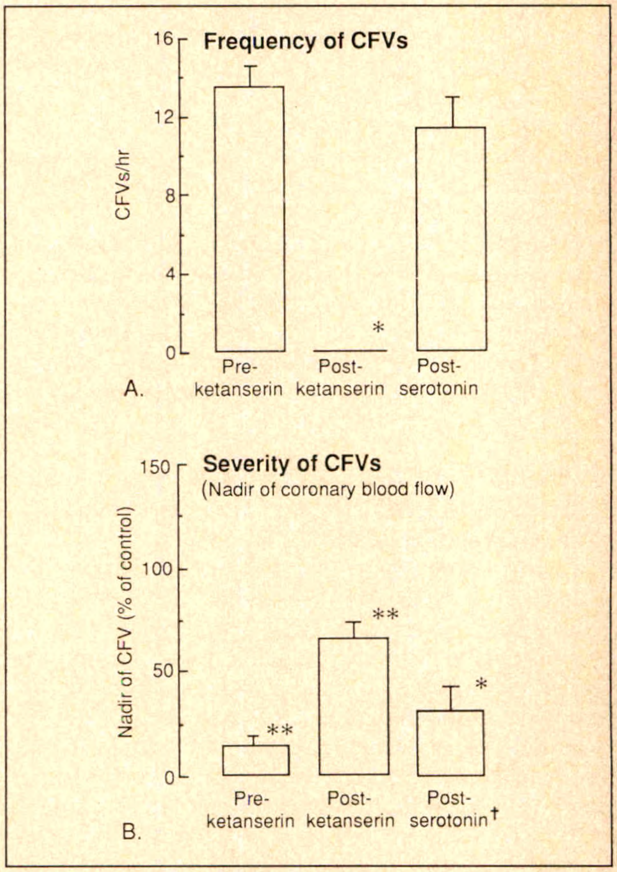

FIGURE 4. *A*, The number of cyclic coronary artery flow variations/hour in dogs during a control period, after abolition of cyclic coronary flows by ketanserin (a serotonin receptor antagonist) and after reestablishment of cyclic coronary artery flows by the infusion of serotonin given as 1-3 μg/min directly into the left atrium. *B*, The severity of coronary flow variations, obtained by averaging the 2 lowest mean flow velocity values (nadirs) as a percentage of controlled unconstricted blood flow velocity over a 30-minute interval, are shown during the control period of cyclic flows and after the serotonin receptor antagonist, ketanserin, had abolished cyclic alterations in coronary blood flow. The severity of cyclic coronary flows after their restoration by serotonin administration is shown in the *far right*. *p <0.05, significantly different from coronary blood flow velocity during infusion of serotonin and before coronary flow variations were restored. **p <0.05, significantly different from control, unconstricted coronary blood flow velocity. †The mean flow velocity nadir in serotonin-restored coronary flow variations was taken as a percentage of mean flow velocity after infusion of serotonin but before the restoration of coronary flow variations. CFV = coronary flow variation. (Adapted from *Circulation*.[24])

TABLE II Growth Factors Potentially Associated with Marked Intimal Proliferation After Endothelial Injury at Sites of Coronary Artery Stenosis

Platelet-derived growth factors
Transforming growth factors
Serotonin
Epidermal growth factors
Fibroblast growth factors
Heparin-associated growth factors
Insulin-like growth factors
Endothelin

alterations. Interfering with both is virtually always protective.[26] Thus, both thromboxane and serotonin are important for initiating or sustaining cyclic flow reductions in this experimental model.[26] If the contribution from both thromboxane and serotonin receptor stimulation is eliminated, cyclic coronary flows are very difficult to restore, even if systemic epinephrine concentrations are markedly increased.[27]

Recently, it has been demonstrated that subsets of patients with limiting angina and significant coronary artery disease have increased transcardiac serotonin concentrations.[13] Moreover, subsets of patients with limiting angina have a vasoconstrictor substance in their coronary sinus effluents whose vasoconstrictor effect is blocked by a serotonin receptor antagonist.[14]

CORONARY ARTERY STENOSIS AND ENDOTHELIAL INJURY IN CLOSED-CHEST, AWAKE, UNSEDATED DOGS

Chronically instrumented, awake, unsedated dogs develop cyclic coronary flow variations or persistently reduced coronary blood flow 2 to 7 days after their original instrumentation with an external coronary artery constrictor and the resultant endothelial injury.[28] Cyclic coronary flow variations or a low-flow state are seen in these animals. There is a continuum between these states and the complete stoppage of coronary blood flow, which is associated with a coronary artery thrombus. Cyclic coronary flow variations and the low-flow state are often reversed to normal coronary blood-flow patterns by thromboxane and serotonin receptor antagonists in this experimental model,[28] just as they are in open-chest, anesthetized animals.[19-27]

The awake, unsedated, closed-chest dog may develop cyclic coronary-flow alterations or a severe and sustained reduction in coronary blood flow when excited by the presence of a person, by food or by low-level exercise.[29] This suggests that excitement and low-level effort may contribute to platelet aggregation with consequent mechanical obstruction and dynamic reductions in coronary blood flow when coronary artery stenosis and endothelial injury coexist. Again, thromboxane and serotonin receptor antagonists usually prevent the cyclic coronary-flow alterations caused by low-level exercise in this model.[29]

One to 3 weeks after the application of the coronary artery constrictor and the endothelial injury, and after frequent cyclic coronary flow alterations, chronically instrumented dogs develop marked intimal proliferation that converts moderately severe coronary artery stenosis to more critical stenosis.

Similar intimal proliferation has been described in endothelially injured carotid arteries in the rat,[32] and in the patient who develops restenosis after coronary artery angioplasty.[33] The marked intimal proliferative responses found in the stenosed coronary artery with endothelial injury and chronic cyclic coronary flow alterations in the awake, unsedated dog and in patients with restenosis after coronary artery angioplasty may be caused by the accumulation of selected growth factors from aggregating platelets or infiltrating white blood cells and activated T cells, including 1 or more of the following (Table II): platelet-derived growth factors, transforming growth factors, epidermal growth factor, fibroblast growth factor, serotonin, endothelin or a heparin-associated growth factor.[34-39] Further studies are needed to test this suggestion and to identify which growth factor(s) and cell population(s) contribute to the fibroproliferative reaction.

CLINICAL IMPLICATIONS AND FUTURE PREDICTIONS

If platelet aggregation and the consequent release of thromboxane and serotonin are important in initiating or sustaining selected acute coronary artery disease syndromes, including unstable angina, an intervention that interferes with platelet aggregation and the subsequent release of thromboxane or serotonin, or both, should reduce morbidity and mortality in patients with unstable angina. Clinical studies[40,41] have shown that aspirin—an inhibitor of cyclooxygenase, thromboxane synthesis and platelet aggregation—reduces the risk of subsequent nonfatal myocardial infarction and death in patients with unstable angina. Specifically, a multicenter Veterans Administration Medical Center study established that in men aspirin (325 mg/day) reduces mortality and the risk of nonfatal myocardial infarction in the weeks after onset of unstable angina.[40] A Canadian study[41] demonstrated that the equivalent of 4 aspirin tablets/day reduces mortality and the risk of subsequent nonfatal myocardial infarction in the ensuing 2 years in men and women with unstable angina. These data are consistent with the hypothesis that in humans platelet aggregation and subsequent increases in local thromboxane and serotonin concentrations may play a role in the abrupt conversion from chronic to acute coronary artery disease syndromes through thromboxane and serotonin accumulation, leading to further platelet aggregation, coronary vasoconstriction and, sometimes, the development of occlusive coronary thrombi (Fig. 1).

Available data from clinical and experimental animal studies are consistent with the hypothesis that interference with thromboxane and serotonin's contributions to platelet aggregation and dynamic coronary artery constriction may prevent conversion from chronic to acute coronary artery disease syndromes, including the development of unstable angina and myocardial infarction in at least some patients at risk. Substantial protection pre-

venting the conversion from stable to unstable angina and myocardial infarction may very well require both thromboxane and serotonin receptor antagonists or the combination of a thromboxane synthesis inhibitor and receptor antagonist with a serotonin receptor antagonist. Future clinical studies should test this hypothesis directly.

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Correlations Between Fibrinolytic Function and Acute Myocardial Infarction

Björn Wiman, MD, PhD, and Anders Hamsten, MD, PhD

The diurnal variation of tissue plasminogen activator and plasminogen activator inhibitor—2 important factors in regulation of fibrinolysis—is well established, but its clinical implications are not yet fully understood. Fibrinolytic function was measured in a group of 133 patients <45 years of age, 3 months after they presented with myocardial infarction, and they were compared with an equal group of carefully matched control subjects. A subsample of 71 patients and 50 control subjects was examined 3 years later. Tissue plasminogen activator inhibitor plasma levels were higher in patients versus control subjects at 3 months and at 3 years after myocardial infarction, with a high degree of correlation between the 2 determinations (r = 0.87). Of all hemostatic parameters studied, only low tissue plasminogen activator activity and increased tissue plasminogen activator inhibitor levels were significantly different between patients with and without recurrent infarction during the 3-year period. In those patients with a second infarction >3 years later, however, tissue plasminogen activator inhibitor concentration was not significantly related to reinfarction.

(Am J Cardiol 1990;66:54G–56G)

Release of tissue plasminogen activator (t-PA) from the vessel wall and the plasma concentration of plasminogen activator inhibitor-1 (PAI-1) are 2 important factors in the regulation of in vivo fibrinolytic function.[1] An impaired function of the fibrinolytic enzyme system is frequently observed in patients with thrombotic disease, either due to decreased release of t-PA from the vessel wall endothelial cells, or, more commonly, to increased plasma PAI-1 levels, or a combination of both.[2,3] The fibrinolytic activity is subjected to a circadian variation with a minimum early in the morning and a peak in the evening. This phenomenon has been known for 30 years, but it is only lately, with the discovery of PAI-1 in plasma[4,5] and the availability of specific methods for measuring t-PA and PAI-1, that it has been studied in greater detail.[6,7] The reason for the circadian variation is, however, not fully understood, but it seems that the variation in PAI-1 levels is more pronounced than that of t-PA levels, with peak levels occurring around 4 A.M. to 6 A.M., when fibrinolytic activity is lowest.

In the current summary we will discuss our results regarding fibrinolytic function in a group of patients presenting with myocardial infarction (MI) before the age of 45. The investigation started as a case-control study, and was subsequently continued as a prospective study of recurrent myocardial infarction.[8–10]

METHODS

Postinfarction patients were subjected to hemostatic and metabolic evaluation about 3 months after the MI, along with carefully matched control subjects. Blood samples were drawn in the morning from the patients and their control subjects on the same occasion.[8] A subsample of both patients and control subjects was investigated for hemostatic parameters 3 years later.[9] All patients were also followed to identify recurrent infarction.[10]

PAI-1 activity was measured by inactivation of single-chain t-PA[11] and the activity expressed in arbitrary units (AU) corresponding to international t-PA units (IU). Determination of t-PA was performed by a coupled spectrophotometric assay using soluble fibrin as stimulator.[11] The t-PA antigen was measured with a double antibody radioimmunoassay.[12]

Unfortunately, no specific method for determination of t-PA activity was available at the time of the baseline investigation. Therefore, on that occasion, plasminogen activator activity was determined by the fibrin plate assay using euglobulin precipitates. Urokinase was used as a standard and the results expressed in Plough units (PU).

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TABLE I Fibrinolytic Parameters in Young Myocardial Infarction Patients in Blood Samples Drawn Three Months and Three Years After the Event*

	3 Months		3 Years	
No.	Pts (133)	Control Subjects (133)	Pts (71)	Control Subjects (50)
PA activity after occlusion (PU/ml)	0.29 ± 0.03[†]	0.58 ± 0.04	—	—
t-PA activity after occlusion (IU/ml)	—	—	3.2 ± 0.6[‡]	9.0 ± 1.5
t-PA antigen μg/L				
Before occlusion	—	—	5.8 ± 0.2[‡]	4.9 ± 0.2
After occlusion	—	—	14.3 ± 0.7[‡]	15.9 ± 1.2
PAI-1 before occlusion (AU/ml)	17.3 ± 1.2[‡]	10.5 ± 0.7	16.0 ± 1.6[‡]	7.5 ± 1.1

[*] Data from matched control subjects are included for comparison. All data are mean ± standard error of the mean.

[†] $p < 0.01$, [‡] $p < 0.001$ on comparison with control subjects.

AU = arbitrary units; PA = plasminogen activator; PAI-1 = plasminogen activator inhibitor; PU = Plough units; t-PA = tissue plasminogen activator.

TABLE II Fibrinolytic Parameters and Fibrinogen in Young Myocardial Infarction Patients With and Without Recurrences*

Component	Uneventful Course (90)	Early Reinfarction (19)	Late Reinfarction (18)	p Value
Fibrinogen (g/liter)	3.5 ± 1.0	3.8 ± 1.2	3.5 ± 1.1	NS
PAI-1 (AU/ml)	17.9 ± 13.4	26.6 ± 16.7	18.7 ± 11.4	<0.05
Plasminogen activator activity (PU/ml)	0.32 ± 0.46	0.08 ± 0.07	0.24 ± 0.32	<0.05

[*] The samples were drawn about 3 months after the first event. The data are given as mean ± standard deviation and differences between the groups evaluated by analysis of variance.

NS = not significant, other abbreviations as in Table I.

RESULTS AND DISCUSSION

The results of measurements of fibrinolytic variables in patients 3 months and 3 years after MI are summarized in Table I.

At 3 months after MI, the patient group had significantly decreased ability to release plasminogen activator activity on venous occlusion as compared to the control subjects. Since no precautions were taken during blood sampling for the fibrin plate assay to prevent inactivation by PAI-1 present in the plasma, these results were most likely determined by increased PAI-1 levels in the samples. Indeed, the patient group had markedly increased PAI-1 levels as compared to the control subjects.

At 3 years after MI, the fibrinolytic disturbances persisted in the patient group, with increased plasma PAI-1 concentration and low t-PA activity in samples both before and after venous occlusion as compared to the control subjects. In contrast to t-PA activity, no difference was observed regarding t-PA antigen levels, either in preocclusion or postocclusion samples. The specific activity of the released t-PA in the healthy individuals was close to the theoretical value for fully active t-PA but only about 30% of full activity in the patient group. This indicates that a major portion of the released t-PA in the patients becomes rapidly neutralized by PAI-1.

The PAI-1 levels in plasma were highly increased both 3 months and 3 years after MI with a high degree of correlation (r = 0.87) between the 2 determinations. This certainly indicates that the elevated PAI-1 levels were not merely a result of an acute phase response, which may also influence plasma PAI-1 levels.[13] This notion is also supported by the fact that the connection between PAI-1 levels and MI persisted also after multivariate statistical analysis with orosomucoid (acidic α_1-glycoprotein) concentration included in the model.

PAI-1 concentrations correlated positively with serum triglyceride levels and the weight/height ratio, which is in agreement with data from other groups.[14] In addition, insulin levels seem to correlate with PAI-1 concentrations.[14] On dividing the patient group according to lipoprotein phenotype, it appeared that the patients with hypertriglyceridemia had more than threefold elevated PAI-1 levels as compared to the normolipoproteinemic control subjects. In contrast, in the normolipoproteinemic patients a lesser ability to release t-PA on venous occlusion was relatively more frequent.

Currently, 127 male patients without severe concomitant disease have been included in the study and followed for at least 5 years. During this time, 37 patients suffered reinfarctions, of which 19 were within 3 years of the first MI and 18 were later (3 to 8 years after the first event). The results of fibrinolytic parameters at 3 months after the first MI in these groups are summarized in Table II.

Of all the hemostatic factors studied, only a low PA activity after venous occlusion and increased PAI-1 levels were significantly different between the patients with and without recurrences within 3 years. Fibrinogen levels tended to be different but failed to reach significance (p = 0.08). The statistical difference in PAI-1 levels persisted also after multivariate analysis, when lipids, coronary atheromatosis score and left ventricular function (ejection fraction) were included. However, in those patients with a second MI more than 3 years after the first event, the PAI-1 concentration was no longer significantly related to reinfarction. Currently, the reason for this is not known, but 1 explanation might be that the cause of increased PAI-1 levels 3 months after MI differs among the patients and that a subpopulation only temporarily has increased levels. Perhaps, analysis of PAI-1 concentration must be performed on several occasions to detect those subjects with constantly elevated levels. More work is needed to clarify this point.

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Propranolol and the Morning Increase in Sudden Cardiac Death: (The Beta-Blocker Heart Attack Trial Experience)

Robert W. Peters, MD

To provide insight into the protective effect of propranolol on mortality after myocardial infarction observed in the β-Blocker Heart Attack Trial, the time of occurrence of sudden cardiac death was examined in this population. Between 5 A.M. and 11 A.M., 25 of the 56 total deaths (38%) occurred in the placebo patients compared with 11 of 45 (24%) in the propranolol patients. Excluding this period, there were nearly equal numbers of sudden cardiac deaths in the propranolol and placebo groups. This retrospective analysis suggests that β blockade is protective during the morning hours when a surge of sympathetic activity may increase the risk of sudden cardiac death.

(Am J Cardiol 1990;66:57G–59G)

Sudden cardiac death (SCD), which causes approximately one-sixth of all deaths in the United States, is a major problem confronting contemporary cardiology.[1] More detailed information about its pathogenesis is mandatory if specific preventive measures are to be developed and implemented. Recent evidence suggests that SCD is more frequent during the midmorning hours.[1,2] Similar midmorning peaks are found in the onset of myocardial infarction and transient myocardial ischemia.[3-5] The available data implicate increased sympathetic nervous system activity associated with awakening and assuming the upright posture in the pathogenesis of these disorders. Beta blockers have been shown to diminish the morning peaks in the occurrence of transient myocardial ischemia, and myocardial infarction does not appear to have a prominent morning peak in patients taking β-blocking agents before onset of infarction.

The β-Blocker Heart Attack Trial (BHAT) and other studies have demonstrated that β-adrenergic blocking agents prevent SCD and recurrent myocardial infarction,[6,7] although the mechanism of this beneficial effect has not been identified. Accordingly, we examined the time of occurrence of SCD in the large and carefully followed population of the BHAT to determine: (1) if a morning increase existed in patients not receiving β blockers and (2) whether this increase, if present in the placebo group, would be eliminated in those randomly assigned to β-blocker therapy. A full report of this experience has recently been published.[8]

METHODS

The BHAT was a randomized, double-blind, placebo-controlled study of propranolol in the prevention of mortality and morbidity after acute myocardial infarction. Recruitment of 3,837 subjects was carried out between June 1978 and October 1980. A detailed description of materials and methods has been published.[6] Briefly, patients aged 30 through 69 were randomized to either propranolol (180 or 240 mg/day) or placebo, 5 to 21 days after admission for acute myocardial infarction. Specifically excluded were patients with either an indication (e.g., postinfarction rest angina) or a contraindication to the use of β blockers. After hospital discharge, patients were seen in follow-up at regular intervals.

All deaths were reported on a mortality form that included a copy of the death certificate, information about acute and prodromal signs and symptoms, as well as postmortem examination results, when available. Information about deaths was obtained by the participating

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clinical centers through interviews with family members, bystanders at the scene of death and primary care physicians. The mortality forms were analyzed by a Mortality Classification Committee, and deaths were coded according to preset guidelines by 2 committee members. Disagreement between coders was resolved by a vote of the entire committee. All individuals involved in filling out or coding forms or care of BHAT patients were blinded as to treatment group. SCD was defined clinically, based, in part, on chronology, and not necessarily on definitive evidence of an arrhythmic mechanism or autopsy data, since these data were frequently nonexistent. Death was considered to have occurred at the time of "clinical death," rather than the time listed on the death certificate. Clinical death was defined as spontaneous cessation of respiration and blood circulation with loss of consciousness from which there was no recovery, regardless of cardiopulmonary resuscitation efforts. Thus, if a patient collapsed and never regained consciousness after prolonged cardiopulmonary resuscitation, clinical death occurred at the time of original collapse, even if the patient remained "alive" for another 3 days. The timing of clinical death was estimated to the nearest hour. In situations where this estimate was impossible (e.g., a patient who lived alone and was last seen 2 days earlier), the individual was excluded from analysis. For purposes of this study, SCD included out-of-hospital deaths that were either instantaneous or occurred within 1 hour of the onset of symptoms.

RESULTS

There were 56 out-of-hospital SCDs in the placebo group compared with 45 in the group receiving propranolol. The majority of these deaths in both groups occurred at home. As shown in Figure 1, from 5 to 8 A.M. there were 6 deaths in the placebo group compared with none in the propranolol group. Excluding the 6-hour period between 5 and 11 A.M., there were nearly equal numbers of SCDs in the propranolol and placebo groups.

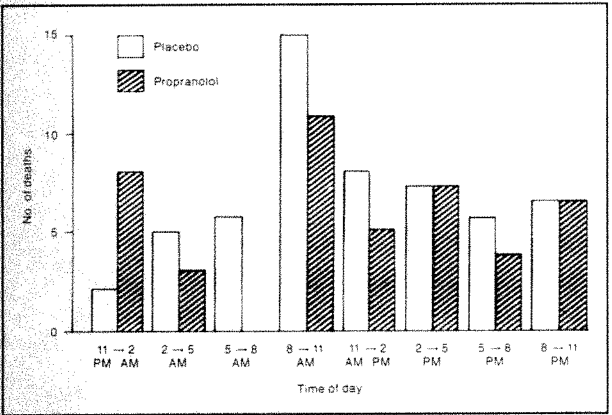

FIGURE 1. The distribution of deaths over a 24-hour period grouped in 3-hour intervals (e.g., 2 to 5 A.M. = the number of deaths between 2 A.M. and 4:59 A.M., etc.). (Adapted from *Am J Cardiol.*[8])

DISCUSSION

Our findings in the BHAT placebo group confirm previous observations that SCD displays a morning increase with a peak in the midmorning hours.[1,2] In addition, our study provides the first evidence that β blockers prevent or blunt this midmorning peak. Our observations are of particular interest in light of the fact that, as previously reported, ventricular arrhythmias in BHAT did not display a midmorning peak but, in fact, were elevated throughout waking hours.[9] This dissociation between arrhythmias and SCD suggests that SCD in postinfarction patients is not purely arrhythmically mediated and that factors triggering the onset of coronary thrombosis and myocardial ischemia may have an important role in pathogenesis.

Study limitations: Our findings must be interpreted in light of certain limitations. First, data analysis was performed retrospectively, so certain biases inherent in retrospective studies are possible. However, the data were obtained and tabulated prospectively and the time of death was determined without knowledge as to treatment group, so systematic bias is unlikely. Second, our conclusions apply only to SCD occurring outside of a hospital. We chose to analyze only this select group because hospitalized patients often have events or interruptions that affect the daily activity cycle (for example, being awakened in the early morning hours for medication administration, receiving intravenous lidocaine for treatment of ventricular ectopy and so on). Third, the timing of an event is somewhat subjective, since critical information is often unavailable. For this reason, we routinely excluded deaths where the timing (to the nearest hour) was uncertain. Fourth, we do not have complete information on several other factors, including medication compliance, the time that patients ordinarily took their medication (or even whether they took it at all in the days and hours preceding death), the time of awakening on the day of death and their usual waking and sleeping hours. Thus, it is possible that our data underestimate the protective effect of β blockers.

CONCLUSION

Analysis of the timing of out-of-hospital SCD in the BHAT placebo group revealed a midmorning peak that was less prominent in the patients receiving propranolol. These observations add to the growing evidence that increased activity of the sympathetic nervous system associated with awakening may trigger the onset of cardiovascular events, and that β blockade may be of benefit by severing the linkage between a potentially triggering event and its cardiac consequences. This hypothesis could be tested by analysis of the time of cardiac events in past and future large-scale, randomized studies of β-blocker therapy.

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Beta-Blocker Duration of Action and Implications for Therapy

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Two studies were conducted to measure the effect of serum half-life on β-blocker–related heart rate reduction throughout the 24-hour period. In the first study, nadolol, atenolol and pindolol were associated with significant (p <0.01) heart rate reduction even at 24 hours after dose. Nadolol, with a plasma half-life of 15.5 hours, had the most pronounced heart rate-lowering effect 24 hours after the daily dose compared to pindolol, which had a half-life of 5.5 hours. In a randomized, double-blind, crossover study, nadolol and atenolol had similar effects 3 to 4 hours after the daily dose. Nadolol, however, produced greater suppression of heart rate and double product (blood pressure × heart rate) than atenolol (compared to placebo) 24 hours after ingestion of the daily dose. On ambulatory electrocardiography 24 hours after medication administration, 80 to 100% of the heart rate-attenuating effect of nadolol was maintained versus only 20 to 45% of atenolol's effect. Statistically significant (p <0.05) reductions in heart rate were produced by nadolol, but not by atenolol, between 4 and 5 A.M., 6 and 7 A.M., 8 and 9 A.M. and 9 and 10 A.M. Furthermore, nadolol remained at 52% of peak blood level at 24 hours, whereas atenolol was at 20%. The data from these 2 studies indicate that significant differences in duration of action exist between β blockers.

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There is good evidence for beneficial effects of β-blocker therapy on the circadian pattern of ischemic events. Recent studies have provided convincing evidence that β blockade is effective in reducing blood pressure, frequency of occurrence of angina and silent myocardial ischemia and the morning peak in ischemic episodes.[1–4] Beta blockers, however, differ in terms of important properties such as serum half-life. We conducted 2 studies[5,6] to determine whether nadolol, atenolol and pindolol provide equal "early" (3 to 4 hours after dose) and "late" (24 hours after dose) effects during once-a-day administration.

COMPARISON OF NADOLOL AND PINDOLOL

The benefit of β blockers in the symptomatic treatment of angina on effort is mediated primarily through a decrease in double product (heart rate × blood pressure) during submaximal exercise.[5,7] Although the effects of β blockers are not directly related to their blood concentrations we have found fairly good linear relations between the logarithm of β-blocker blood level and pharmacodynamic effects on heart rate.[5]

Adult men with at least 5 attacks/week of angina on effort caused by coronary artery disease were included in the study. Patients with myocardial infarction or aortocoronary bypass surgery within the preceding 3 months were excluded, as were patients for whom β blockade was contraindicated. The nadolol group was composed of 18 patients receiving 40 to 160 mg once daily and the pindolol group consisted of 11 patients receiving 40 to 160 mg once daily. After a 4-week, single-blind, placebo period, active drug treatment was initiated with biweekly upward dosage titration until 50% reduction in spontaneous angina attacks or unacceptable side effects occurred. Exercise treadmill tests were performed at the beginning and end of the placebo period and then every 2 weeks thereafter. A late test was performed just before ingestion of the daily dose (i.e., 24 hours after the preceding dose) and an early test was performed 2 to 3 hours after ingestion of the daily dose. In addition, blood pressure, heart rate, exercise tolerance and magnitude of ST-segment depression were recorded at rest, at the end of each exercise stage and at maximal exercise.

The 2 β blockers effectively decreased spontaneous angina frequency (p <0.05) and increased exercise tolerance on the treadmill (p <0.05) compared to placebo. Slightly lower (not statistically significant) exercise tolerance occurred at late testing compared with early testing for both drugs.

Significant (p <0.01) depression of heart rate response was observed using each of the 2 β blockers during

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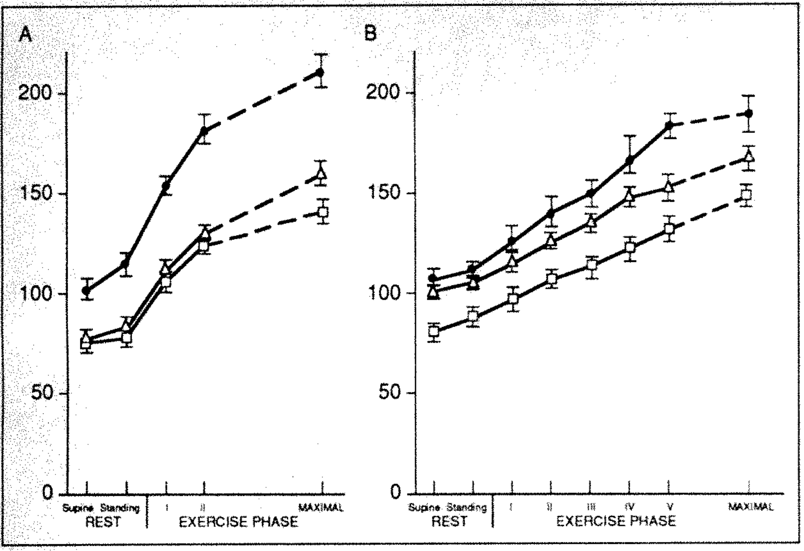

FIGURE 1. Effect of nadolol (*A*) and pindolol (*B*) on exercise double product at 3 hours (*squares*) and 24 hours (*triangles*) after dose in comparison with placebo (*dots*). (Adapted from *Am Heart J*.[5])

early exercise stress testing. Exercise heart rate depression was still observed during late testing. Nadolol treatment, however, was associated with greater attenuation of maximal heart rate 24 hours after medication administration. Figure 1 illustrates the effects of nadolol and pindolol on exercise double product. Although not significant, a trend toward more pronounced ST-segment depression at maximal exercise on late (24-hour) stress testing was observed in both treatment groups.

A linear relation was observed between the logarithm of β-blocker plasma concentration and heart rate at submaximal exercise. As the plasma β-blocker concentration declined with time (after medication administration), the submaximal-exercise heart rate increased. The plasma half-life of nadolol in this study was 15.5 hours and that of pindolol was 5.5 hours, and the heart rate-lowering was more pronounced for a longer period with nadolol compared with pindolol.

COMPARISON OF NADOLOL AND ATENOLOL

Given that the serum half-lives of the once-daily β blockers, nadolol and atenolol, vary, a randomized, double-blind, crossover study[6] was conducted to compare their effects 3 to 4 hours and 24 hours after the daily dose. Nineteen men and 4 women who had classic angina occurring no less than 5 times/week participated in the study. Antianginal therapy was withdrawn over a 2-week period. The study consisted of 3 periods: a placebo run-in period; a randomized, double-blind, active-therapy period; and a double-blind, crossover (active therapy) period.

During the first 2 weeks of the placebo run-in period, all antianginal medications were withdrawn. During the final 2 weeks, all antianginal therapy except for nitroglycerin (for pain, not prophylaxis) was discontinued. Test results of week 4 were used as baseline values.

The randomized, double-blind, active-therapy period lasted 4 weeks. For the first 14 days, random assignment was made to nadolol 40 mg or atenolol 50 mg. Treatment was increased to 80 mg nadolol or 100 mg atenolol after 14 days, if angina frequency was not reduced by ≥50% compared with baseline.

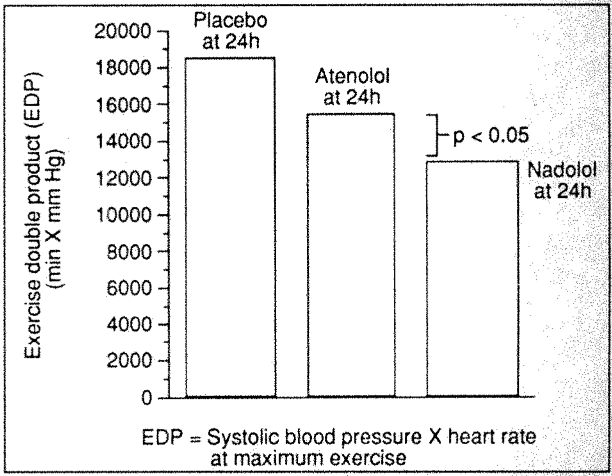

FIGURE 2. Effect of atenolol and nadolol on exercise double product (EDP) 24 hours (h) after dosing. (Adapted from *Am J Cardiol*.[6])

During the 2-week, double-blind, crossover period, the patients receiving 50 mg atenolol at the end of the previous period were assigned 40 mg nadolol and vice versa. Similarly, the patients receiving higher doses of the 2 agents were switched accordingly. The mean dose of atenolol was 69 ± 25 mg and of nadolol 55 ± 20 mg.

At the end of each study period, exercise stress tests were conducted at estimated peak (approximately 3 to 4 hours) and trough (approximately 24 hours) drug blood levels. Before the initiation of exercise testing, venous blood was drawn to measure drug levels. Sixteen patients completed all 3 phases of the study.

Approximately 3 to 4 hours after the daily dose, both nadolol and atenolol were associated with prolonged exercise time on the treadmill. There were no significant differences between the 2 agents' effects on the exercise variables (supine, standing, submaximal- and maximal-exercise heart rates and double products).

When testing was performed 24 hours after ingestion of the daily morning dose, the suppression in heart rate and double product compared with placebo was more pronounced during nadolol treatment compared with atenolol treatment (Fig. 2). Statistically significant differences between the β blockers' effects on supine, standing and maximal-exercise heart rates and for maximal-exercise double products were present.

While the 2 agents did not differ significantly in their effects on heart rate in the late morning, evening and night hours, nadolol was more effective in the hours just before and after ingestion of the daily dose. In essence, nadolol continued to effectively lower heart rates even before plasma drug levels were expected to reach peak values. Between 4 and 5 A.M. and 6 and 7 A.M., these differences compared to placebo were statistically significant ($p < 0.05$) for nadolol but not for atenolol. Between 8 and 9 A.M. and 9 and 10 A.M., heart rates were significantly lower ($p < 0.05$) for nadolol than for atenolol.

The different pharmacokinetic properties of the 2 β blockers may account for the observed differences between the 2 agents. The estimated half-life of nadolol was 23.93 ± 7 hours compared to 8.87 ± 1.03 hours for atenolol. Nadolol's half-life was more than twice as long as that of atenolol. Furthermore, 24 hours after dose administration, nadolol remained at 52% of peak blood level versus 20% of peak blood level for atenolol.

Both agents were found to be effective ($p < 0.0001$) in decreasing angina frequency (tabulated attacks/week) compared with placebo. In this respect, there was no statistical difference between the 2 drugs. The fact that atenolol was not associated with significantly higher angina frequency despite lower blood levels in the morning hours may be a result of the study's low power to examine differences in angina frequency hour by hour.

CONCLUSIONS

These 2 studies indicate that while patients are receiving once-a-day administration, agents such as the β blocker nadolol, which have been shown to have longer pharmacodynamic half-lives, can produce significant reduction in exercise parameters throughout the full 24-hour dosing interval, including the vulnerable morning hours. Suppression of double product was more pronounced for nadolol than atenolol at 24 hours after the dose. In β-blocker therapy it is important to consider an agent's half-life among other properties, since there appear to be significant differences in duration of action between β blockers that have been defined as long-acting. These differences may have clinical significance, since ischemic events (both overt and silent) tend to occur more frequently in the morning hours.

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Effect of Beta-Adrenergic Blocking Agents on the Circadian Occurrence of Ischemic Cardiovascular Events

Sidney Goldstein, MD

Clinical observations suggest that β-adrenergic blocking agents can modify the circadian occurrence of a variety of ischemic events. Morning awakening is associated with a rapid increase in blood pressure and pulse, serum catecholamine content and platelet activation, at a time of decreased blood thrombolytic activity. Beta-adrenergic blocking agents have the potential to modify many of these events. Current data indicate that these agents modify blood pressure and pulse, but do not prevent their early morning increase. In addition, β-adrenergic blocking agents decrease ventricular ectopy and its circadian variation. Recent studies in humans indicate, however, that metoprolol does not affect the circadian increase in platelet activity or serum catecholamines. The specific mechanism by which β blockers affect the circadian occurrence of ischemic events remains uncertain.

(Am J Cardiol 1990;66:63G–65G)

Recent observations have drawn attention to a circadian occurrence of acute ischemic events, including angina pectoris,[1] acute myocardial infarction[2] and sudden death.[3] This increased morning circadian event rate in patients with ischemic heart disease has provided a stimulus for consideration of the temporal occurrence of acute ischemic syndromes in a number of clinical settings.

In addition to calling attention to the temporal occurrence of ischemic cardiac syndromes, Muller et al[2] reported a modulating effect of β-adrenergic blocking agents on the circadian occurrence of acute myocardial infarction. They reported that patients receiving a β-adrenergic blocking agent before their acute myocardial infarction had a reduction of the early morning peak in the occurrence of that event. This observation suggests a link between the pathophysiologic effects that occur on awakening and their potential modification by β-adrenergic–blocking agents.

These observations are supported by a retrospective analysis of the β-Blocker Heart Attack Trial by Peters et al.[4,5] In that study, propranolol treatment appeared to have its major salutary effect on the occurrence of sudden death in the early morning hours in postmyocardial infarction patients. In the placebo patients, 38% experienced sudden death between 5 A.M. and 11 A.M., compared to 24% in the propranolol-treated patients. In the remaining period of the day the occurrence of sudden death was almost equal in both placebo and treatment groups.

In a seminal review, Muller et al[6] described the physiologic factors related to circadian and other triggers of morbid events in cardiovascular disease. A number of neurohumoral and hemodynamic changes have been known to occur in a circadian fashion. The process of morning awakening is associated with increased blood pressure and heart rate.[7] In addition to these hemodynamic changes, adverse modification of neurohumoral and hematologic functions occur that have the potential to initiate the occurrence of acute ischemic events. These include increases in plasma norepinephrine and epinephrine,[8] cortisol[9] and platelet aggregability,[10] at a time when low levels of tissue-type plasminogen fibrinolytic activity are present.[11]

How β-adrenergic blocking agents modify these ischemic events is uncertain. The role of β-adrenergic blocking agents on angina pectoris has provided some insight into these mechanisms. Prager et al,[12] using a β_1-selective blocker, demonstrated a significant reduction in the circadian frequency of ischemic episodes during treatment.

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Studies with metoprolol[13] and atenolol[14] have also demonstrated a decrease in the occurrence of symptomatic and asymptomatic ischemia throughout the day. They appear to have a particular effect on modifying the early morning occurrence of ischemic events. Cohn et al[15] and Peters et al[16] examined the effect of long-acting propranolol on silent myocardial ischemia and sudden cardiac death respectively, and observed a benefit throughout the day and a reduction of the morning circadian peak. It is clear that β-adrenergic blocking agents have a salutary effect on angina and attenuate its circadian occurrence. There appear to be at least 4 possible mechanisms by which β-adrenergic blocking agents can achieve their effect. Beta-adrenergic blocking agents can modify: (1) blood pressure and pulse rate; (2) clotting mechanisms; (3) catecholamines and their receptors; and (4) cardiac arrhythmias.

HEMODYNAMIC MECHANISM

In hypertensive patients metoprolol decreases the pulse rate and blood pressure, but it does not, however, ablate the circadian variation of blood pressure.[17] In patients with angina pectoris, metoprolol decreases mean systolic and diastolic blood pressure and pulse, but does not change the increase in these parameters on awakening. It is possible, therefore, that these agents achieve their hemodynamic effect by decreasing the overall determinants of myocardial oxygen requirements rather than their sudden change. Alternatively, the beneficial hemodynamic effect of β blockade may be the result of a decrease of peak systolic values, since a decrease of the basal values results in lower peak values even though the morning increases of arterial blood pressure and heart rate remain.

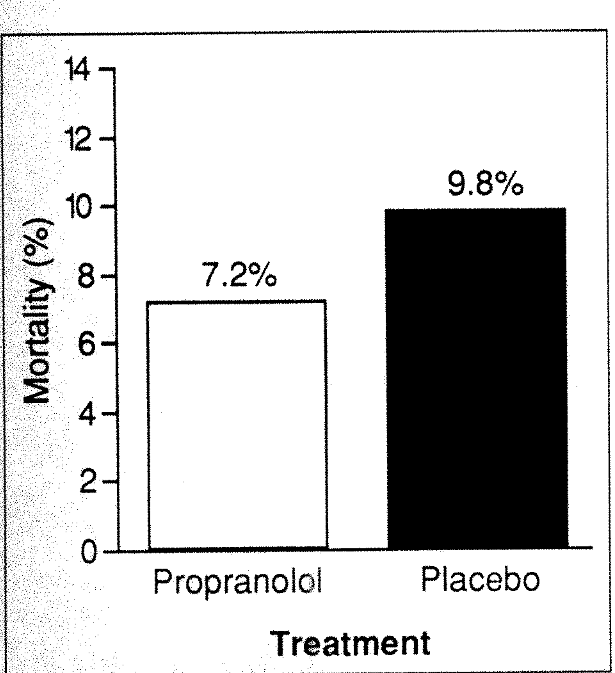

FIGURE 1. Total mortality in the β-Blocker Heart Attack Trial. (Adapted from *J Am Coll Cardiol*.[22])

HEMATOLOGIC MECHANISM

Tofler et al[18] described the association between platelet aggregability and the circadian occurrence of acute myocardial infarction and sudden death. Beta blockers may affect ischemic episodes by modifying the coagulable state of the blood. A number of studies have demonstrated that β-adrenergic blocking agents reduce platelet aggregability and affect coagulation mechanisms in man.[19,20] This area remains controversial, however, since investigations are not without some degree of contradiction.[21] Examination of the effect of metoprolol on circadian platelet activation failed to demonstrate any effect of that drug. These data suggest that either platelet activation as measured by in vitro techniques does not reflect systemic platelet function, or that the salutary effect of β blockers on ischemia is not related to the hematologic mechanism.

NEUROHUMORAL MECHANISM

Recently the interrelation between silent ischemia and catecholamines has been examined in patients with stable coronary artery disease during treatment with metoprolol.[13] Although ischemic events were suppressed with metoprolol, there was no evidence of modification of serum catecholamine concentration during treatment.

ARRHYTHMIA MECHANISM

Beta-adrenergic blocking agents may also exert their salutary effect on sudden cardiac death mortality by modifying ventricular ectopy. These agents suppress the occurrence of ventricular ectopy in normal persons and in patients with ischemic heart disease. Observations in the β-Blocker Heart Attack Trial demonstrate that the decrease in complex ventricular ectopy observed in propranolol-treated patients was associated with a decrease in

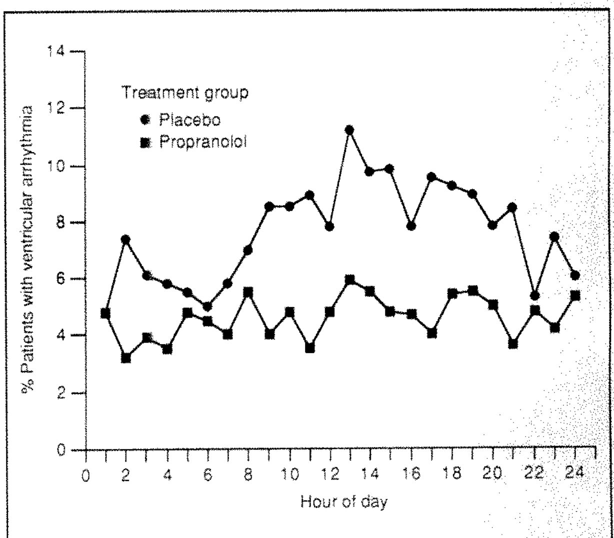

FIGURE 2. Percent of patients in the β-Blocker Heart Attack Trial having ventricular arrhythmias in the placebo and propranolol groups throughout the 24 hours of the day, starting at midnight. (Adapted from *Circulation*.[23])

cardiac mortality (Fig. 1).[22] Of particular interest was the observation that propranolol eradicated the increase in ventricular ectopy that occurred with awakening and persisted throughout the day (Fig. 2).[23] Similar results were observed by Prager et al[12] in patients with ambulatory angina in whom the suppression of the circadian occurrence of ischemia was associated with a decrease in ventricular ectopy. A recent study by Nademanee et al[24] also confirmed the suppression of diurnal variation in ventricular ectopy in nadolol-treated patients.

The importance of the role of acute ischemia and platelet aggregation as a mechanism by which ischemic events occur is emphasized by Davies and Thomas[25] in their autopsy studies of sudden-death victims. How β-adrenergic blocking agents affect this mechanism remains unclear. A number of hypotheses have been proposed. It is clear that these agents modify blood pressure and pulse rate, and therefore decrease the physical intravascular forces that can lead to plaque rupture. In addition, the effect of β blockers on platelet aggregation still remains uncertain. Although several studies have examined the effect of these drugs on platelet activation using in vitro technology, the possibility still exists that these measurements do not accurately reflect in vivo platelet activity.

It is also possible that β-adrenergic blocking agents may affect sudden cardiac death and ventricular fibrillation by modifying ventricular ectopy and ventricular-fibrillation threshold.[26]

Clinical investigations support the benefit of β-adrenergic blocking agents in the prevention of circadian ischemic events. A complete understanding of the interaction between β blockers and acute ischemia remains to be developed. This group of agents not only has provided a therapy by which one can modify these events, but also a pharmacologic probe with which we can examine the mechanism by which they occur.

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Reduction of Mortality, Sudden Death and Non-fatal Reinfarction with Beta-Adrenergic Blockers in Survivors of Acute Myocardial Infarction: A New Hypothesis Regarding the Cardioprotective Action of Beta-Adrenergic Blockade

William H. Frishman, MD, and Eliot J. Lazar, MD

Beta-adrenergic blockers have been shown definitely to reduce the incidence of total mortality, cardiovascular mortality, sudden death and nonfatal reinfarction in survivors of an acute myocardial infarction. The mechanisms to explain this protective action of β blockers have never been elucidated conclusively, and include the antiarrhythmic and myocardial oxygen demand-reducing effects of the drugs. An antithrombotic mechanism has also been suggested. However, β blockers have relatively weak antiplatelet activity, suggesting that their antithrombotic effects may be related to prevention of coronary artery plaque rupture and the subsequent propagation of an occlusive arterial thrombus rather than direct anticoagulant action. The therapeutic ability of β blockers to attenuate the hemodynamic consequences of catecholamine surges, may protect a vulnerable atherosclerotic plaque from fracture, thereby reducing risk of coronary thrombosis, myocardial infarction and death.

(Am J Cardiol 1990;66:66G–70G)

Despite a decline in the incidence of coronary artery disease (CAD) in the United States, more than 600,000 patients are admitted annually to hospitals with a diagnosis of acute myocardial infarction (MI).[1] Even with today's modern therapy, there is a substantial in-hospital mortality followed by an increased morbidity and mortality in the post-hospital period.[2] Patients <70 years of age who survive the in-hospital phase of MI have a 10% mortality rate in the first year after discharge, with the highest proportion of deaths occurring in the first 3 months.[2] Subsequently, there is a 5% annual mortality rate, 6 times higher than the expected rate in an age-matched population without CAD.[2] Approximately 85% of deaths that occur after hospital discharge are related to CAD, most likely from recurrent coronary thrombosis with and without ventricular fibrillation.

Prospective epidemiologic studies have identified subsets of infarct patients with a high, intermediate or low risk of mortality.[3,4] Prolonging life in this heterogenous group of patients is a major goal of preventive therapy. To reach this goal, a variety of therapeutic approaches have been or are being evaluated, including life-style measures (dietary modification, cessation of smoking and physical exercise) and coronary artery reconstructive procedures.[5] Specific pharmacologic agents have included anticoagulants, thrombolytic drugs, drugs that inhibit platelet aggregation, antiarrhythmic drugs, calcium antagonists, angiotensin-converting enzyme inhibitors and β-adrenergic blockers.[5] Among the multiple long-term treatment interventions evaluated to date, β-adrenergic blockade and aspirin therapy have been clearly demonstrated to be efficacious in reducing cardiovascular mortality and nonfatal reinfarction in patients surviving the acute phase of MI.[6]

BETA-ADRENERGIC BLOCKADE IN THE POSTINFARCTION PERIOD

The presumed major mechanisms for increased risk of cardiovascular mortality during the postinfarction period include persistent myocardial ischemia, cardiac arrhythmias, left ventricular dysfunction and recurrent coronary thrombosis.[1–5,7] Elevations in plasma catecholamine levels or enhanced sympathetic drive can increase both the

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severity of myocardial ischemia and the frequency of ventricular arrhythmias. After the clinical introduction of propranolol for therapy of angina pectoris and arrhythmias, it was proposed that a β blocker may favorably influence the natural history of patients with MI by attenuating the undesirable consequences of increased sympathetic nervous system activity.[5,7,8] However, depression of left ventricular function, a major risk factor contributing to mortality after infarction, can be caused by β blockade.[8,9] For this reason, β blockers were initially avoided or used in small doses in patients with MI. Only in the past 10 years have the results of long-term studies demonstrated conclusively the benefit of β blockade in reducing total mortality and nonfatal reinfarction.[5,7,10]

LONG-TERM BETA-BLOCKER PREVENTION TRIALS

Since 1974, 15 major randomized controlled trials with β blockers after acute MI have been reported, with treatment and mean follow-up extending from 9 months to 6 years.[11-30A] Over 18,000 survivors of acute MI were studied in an attempt to document reductions in total mortality, cardiovascular mortality, coronary mortality, sudden death and nonfatal reinfarction. Fourteen of these trials used a placebo-treated control group and had a double-blind design. The time between the infarction and the start of β-blocker or placebo treatment ranged from <24 hours to 7.5 years. In 12 trials, patients in the low- and intermediate-risk groups were studied predominantly,[11-13,15-18,23-30] and in 3 trials, only high-risk patients were evaluated.[14,22]

The results from 12 of the 15 trials showed a lower mortality rate in the β-blocker group than in the placebo group.[11-13,14,16,17,22-24,26-30,30A] In the 3 largest studies, the reduction in mortality with β blockade was statistically significant.[17,23,26,27] In the remaining 7 trials, the results were not conclusive with regard to overall mortality. Combining the results of all 15 β-blocker trials, mortality is reduced by approximately 21%.

Ten of the 11 trials reporting on the incidence of nonfatal reinfarction showed lower rates in the actively treated groups.[5,7,10,20,30A] In only 1 of the trials was this lower incidence statistically significant. A comparison of the effect of treatment on the incidence of nonfatal reinfarction is complicated for many reasons. The diagnostic criteria for infarction differed among the trials, for example, resulting in large differences in incidence. A statistical test for homogeneity, however, indicated that the results of each trial were consistent with those of the others. When all the findings from the 10 placebo-controlled, double-blind trials are pooled, the reduction in nonfatal reinfarction is 22%, a benefit almost identical to that for overall mortality.

It has been suggested that β-blocker treatment should be started on admission to the hospital to reduce the high rate of mortality among in-patients. In general, short-term intravenous treatment trials were designed to provide information about infarct size, arrhythmias and pain relief, not mortality.[7,11,31] However, in 3 large studies in which intravenous β-blocker treatment was followed by oral treatment, a true reduction of about 15% was observed in the in-patient mortality compared with placebo or control.[32-34]

POSSIBLE MECHANISMS OF BENEFIT

Antiarrhythmic effects: An analysis of cause-specific mortality in the β-blocker trials indicates that the reductions in total mortality were caused by a reduction in cardiovascular deaths.[5,7] Although different definitions of sudden death were reported in the trials, a large part of the benefit from β-blocker therapy appears to have stemmed from the prevention of these deaths.[5,7,19] Seven trials reported on sudden death; the rates of sudden cardiac death were lower in the β-blocker group for all 7 trials.[19] Beta-blocker treatment appears to manifest a trend toward a greater overall reduction in sudden cardiac death than in all-cause mortality. The weighted risk ratios for sudden cardiac death vary between 0.15 and 0.84 (mean 0.67), indicating an overall reduction of 33% in sudden cardiac death. Indeed, if sudden cardiac deaths are subtracted from all-cause mortality, the remaining death rate is 3.5% in the intervention group and 4.4% in the control group, which represents an intervention/control risk ratio of nonsudden death of 0.8. Thus, although nonsudden deaths are reduced by 20% in these trials, the sudden cardiac death rate is reduced to a greater extent.

In the 5 largest trials, the intervention/control risk ratio for nonsudden death ranged from 0.75 to 1.02.[17,22,24,26,27] The 2 smallest trials had the most favorable risk ratios of intervention to control—that is, 0.51 and 0.61 for all-cause mortality and 0.25 and 0.15 for sudden cardiac death.[11,30] However, these same studies had intervention/control risk ratios of 1.4 and 2.8 for nonsudden death. Moreover, it may be argued that this unfavorable difference in nonsudden cardiac death may relate to the specific β blocker used; however, a more probable explanation is the potential for chance associated with small patient numbers.

For witnessed instantaneous deaths, an even larger relative benefit from β-blocker therapy was recorded. The reduction was 59% in 1 study,[26] 46% in another[22] and 37% in another,[17] corresponding to an average reduction in instantaneous deaths of 46%. For these 3 trials, the pooled reduction in all-cause mortality was 31%, indicating that the relative reduction in instantaneous deaths is about 50% higher than that in all-cause mortality. When the instantaneous deaths are removed from the all-cause mortality, the pooled reduction in death in the remaining patients becomes 23%, and the relative reduction in instantaneous deaths is twice as great.

Three of the 7 trials obtained 24-hour ambulatory electrocardiographic records on a subset of their participants, both at trial entry and at a subsequent follow-up visit.[17,24,26] The findings of these 3 trials are similar. In the subgroup of survivors who entered the trial with frequent ventricular premature beats, fewer patients taking β blockers demonstrated this type of arrhythmia at a later follow-up visit than did patients in the placebo groups.[24,35,36] Although the recorded episodes of ventricular tachycardia were few in all trials at follow-up, this arrhythmia was less common in patients receiving β blockers than in patients receiving placebo.

In the trials, a higher serum potassium and a shorter corrected electrocardiographic QT interval were noted in patients receiving β blockers compared with those receiving placebo.[21,24,37] Beta blockers have been observed to attenuate transmembrane potassium fluxes in response to high catecholamine levels.[38] Perhaps part of the protective effect of β blockade comes from its ability to preserve normal serum potassium levels, especially in those patients receiving concurrent diuretic therapy.[37]

Antiischemic effects: Given that the incidence of nonsudden cardiac deaths and nonfatal reinfarction were reduced by β blockade in the long-term trials, the antiischemic actions of the drugs also may have contributed to their beneficial effects in the postinfarction period.

Stimulation of cardiac β-adrenergic receptors by endogenous catecholamines increases myocardial oxygen consumption, and can thereby aggravate the ischemic process. Drugs that block the β-adrenergic receptors also reduce the effects of catecholamines and decrease myocardial oxygen requirements by reducing systemic arterial pressure, heart rate and myocardial contractility at rest and during exercise.[5,7] The effects of these drugs on coronary blood flow are less well defined. Beta blockers may decrease coronary blood flow by allowing the unopposed influence of coronary vasoconstrictor impulses to prevail. Furthermore, these drugs may also augment or maintain overall coronary blood flow by slowing the heart rate and increasing diastolic perfusion time.[5,7,39] More controversial are those studies reporting favorable effects of β blockers on myocardial metabolism, the coronary microvasculature, collateral blood flow, the distribution of myocardial blood flow and oxygen-hemoglobin affinity.[5,7,39] One or several of these antiischemic mechanisms may underlie the beneficial effects of β-blocker therapy in survivors of MI.

Thus, although multiple possibilities have been explored to explain the cardioprotective effect of β blockers, there is as yet no generally accepted mechanism for their effect. Such an explanation may result from new information about the role of thrombus formation in myocardial infarction and sudden death.

Prevention of atherosclerotic plaque tears—a new hypothesis to explain cardioprotection: Coronary thrombi, large enough to be detected by angiography, are often associated with tears (fissures) in the caps of atherosclerotic plaques.[40,41] These tears allow blood to penetrate into the arterial wall, leading to thrombus formation within the intima; this may be followed by propagation of thrombosis into the vessel lumen. This process was described over 60 years ago[42–44]; however, its clinical importance was recognized more recently after the microanatomy of coronary thrombi was established by serial histologic sectioning.[45–48] Plaque tears have been recognized in the angiograms of living patients with unstable angina[49,50] and acute MI,[51,52] and in patients resuscitated from sudden cardiac death.[53] Angioscopy in living patients with unstable angina has also confirmed the presence of mural thrombi on torn atherosclerotic plaques in the coronary arteries.[54,55]

Why a plaque becomes susceptible to rupture is not known. It is presumed to be a dynamic, reversible disorder caused by changes in the constituents in the plaque, its blood supply through the vasa vasorum or the functional integrity of the overlying endothelium.[56] Computer modeling of different forms of plaque has shown that the distribution of circumferential tensile stress across the intima is radically influenced by atherosclerotic plaques.[40] Regions of high circumferential stress correlate closely with the sites of intimal tears found on autopsy.[40]

Sudden increases in blood pressure precipitated by physical or mental stress and surges in sympathetic tone could produce hemodynamic changes leading to plaque rupture. These surges in sympathetic nervous activity could also increase platelet aggregability and possibly coronary vascular tone. Beta-adrenergic blockade may modulate or attenuate the consequences of these sympathetic nervous system surges by inhibiting the effects of catecholamines on blood pressure, heart rate and myocardial contractility.

Beta blockers are known to protect a vulnerable aorta from acute dissection, as well as reducing the risk of recurrent dissection.[9] This is accomplished, in part, by the ability of β blockers to reduce blood pressure and myocardial contractility. Comparing propranolol with hydralazine, using Doppler ultrasonography, Spence[57] found that propranolol was more likely to reduce the velocity of blood flow and the likelihood of nonlaminar blood flow in the aorta, thereby reducing turbulence and vortex formation (as heart rate × blood velocity product is a determinant of arterial blood flow disturbance). This effect of β blockers could also reduce the risk of endothelial damage and plaque rupture; subsequent coronary thrombosis would be less likely to occur. In addition, some β blockers also have weak antiplatelet effects that might prevent the development or propagation of clots.[58]

DISCUSSION

Recent clinical and pathologic evidence has conclusively shown that most MIs are due to coronary thrombosis secondary to plaque rupture.[43,47,59,60] With regard to reducing mortality in infarction survivors, studies with antiarrhythmic drugs have revealed no overall benefit on survival or reinfarction, and perhaps an increased mortality risk.[61,62] Controlled studies in postinfarction patients with calcium antagonists, which are potent coronary dilators and antiischemic drugs, have revealed less benefit on survival or reinfarction compared to β blockers, except in a subgroup of patients with non-Q-wave infarctions.[63]

Beta blockers are mildly effective antiarrhythmic drugs and relatively weak antiplatelet drugs. The protective effects of β blockers in patients with myocardial infarction may not just be related to their antiarrhythmic or heart rate-lowering effects as previously thought, but to an indirect antithrombotic action. As proposed in the current report, their cardioprotective action could be related to a prevention of plaque rupture (Fig. 1) and subsequent thrombosis. As evidence continues to mount regarding the circadian variation of acute cardiovascular events,[64] the importance of maintaining pharmacodynamic action over 24 hours may become paramount.

A theoretical model for the triggering and prevention of coronary thrombosis by plaque rupture and its prevention is shown in Table I. Beta-adrenergic blockers may act initially by reducing the occurrence of atherosclerotic plaque rupture. Aspirin and perhaps β blockers, with their antiplatelet effects, possibly protect against the propagation of thrombosis once a plaque rupture occurs. Heparin can prevent propagation of a thrombus with or without aspirin present. Once a thrombus occludes a vessel, thrombolytic therapy can be used to dissolve the clot. Intravenous β blockade could reduce the heightened sympathetic tone of the periinfarction period that may be aggravating the thrombotic process. Vasodilator drugs might also be useful as adjunctive therapy (nitrates, calcium antagonists) to prevent or attenuate vasoconstriction of the coronary arteries induced by the thrombotic process. Maintenance of long-term β-blocker and aspirin therapy after an infarction could prevent subsequent coronary artery plaque fractures and thrombi.

MIs still occur despite the use of β blockade and aspirin in survivors of MI. The reduction in mortality and nonfatal reinfarction with β blockers is about 20 to 25% compared with placebo. There are certainly other mechanical and neurohumoral influences that must be contributing to plaque rupture and thrombus propagation that remain to be investigated.

CONCLUSIONS

Among the drugs available for treatment of hypertension and ischemia, evidence suggests that β blockers may be especially useful. Beta-adrenergic blockers have been shown to reduce the incidence of total mortality, cardiovascular mortality, sudden death mortality and nonfatal reinfarction in survivors of acute MI. They are also useful for reducing mortality during the hyperacute phase of MI when administered parenterally with and without thrombolysis. The protective effects of β blockade probably extend beyond their antiarrhythmic activity and ability to reduce determinants of myocardial oxygen demand. Beta blockers appear to have important antithrombotic properties, not related to direct anticoagulant activity but possibly through indirect means in reducing the risk of coronary artery plaque rupture and the eventual propagation of thrombosis. Studies need to be done to definitively explore the validity of this new hypothesis. Until then, β blockers with or without aspirin, in conjunction with coronary disease risk-factor management, appear to be the most rational approach for reducing the incidence of mortality and morbidity in patients who have survived an MI.

TABLE I Lines of Defense Against Occlusive Coronary Thrombosis

- Prevention of atherosclerotic plaque formation
    - Modification of risk factors for atherosclerosis
- Prevention of rupture of vulnerable atherosclerotic plaque
    - Prevention of surges in adrenergic activity with beta blockers
- Prevention of thrombus formation once plaque is fractured
    - Aspirin and possibly beta blockers
- Prevention of thrombus propagation once thrombus is initiated
    - Heparin, thrombolytic therapy and aspirin
- Dissolution of occlusive thrombus
    - Thrombolytic therapy and aspirin
- Prevention of recurrent plaque fractures and thrombosis
    - Beta blockers, aspirin and possibly diltiazem and verapamil
    - Protection against catecholamine or other neurohumoral surges

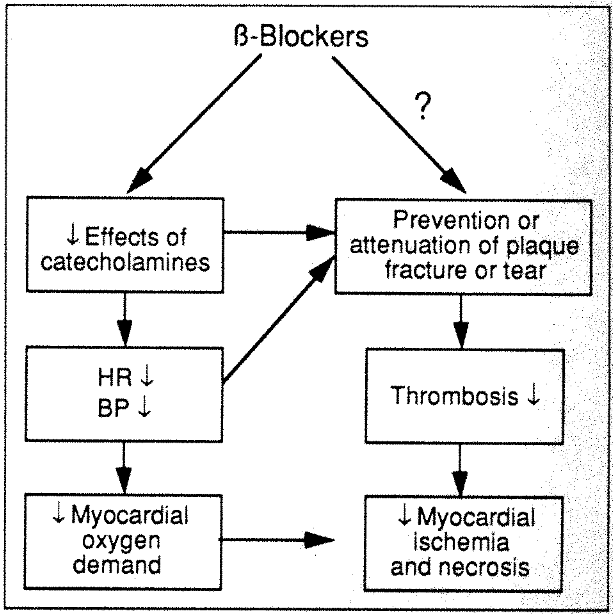
ß-Blockers
?
↓ Effects of catecholamines
Prevention or attenuation of plaque fracture or tear
HR ↓
BP ↓
Thrombosis ↓
↓ Myocardial oxygen demand
↓ Myocardial ischemia and necrosis

FIGURE 1. Proposed role of β-adrenergic blockers in protection against myocardial infarction. BP = blood pressure; HR = heart rate; ↓ = decreasing; ? = unproven.

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